Specification

Pyrazolo [1,5-a] pyrimidine derivatives and NAD(P) H oxidase inhibitor which contains it.

The Field of Technology

This invention relates to the following, namely, a sphere such as for example drug, animal drug (animal industry drug, veterinarian drug, fisheries drug or the like) or the like.

More particularly, it is related to pyrazolo [1,5-a] pyrimidine derivatives and analog to prevent or treat a disease to be related to NAD(P)H and NAD(P)H oxidase inhibitor containing it.

Background Technique

Neutrophil and reactive oxygen species of immunocompetent cell harvest such as for example phagocyte or the like (Reactive oxygen species, ROS) are considered systemically defensively in addition to work (Babior, B.M, N.Engl. J. Med. 298,659-668,721-725,1978) with respect to invaded pathogen when it is worked in tissue destructive in inflammation and circulatory disease (Weiss, S.J, N, Engl. J. Med. 320,365-376,1989.).

Because the origin of main production of ROS by neutrophil was NAD(P)H oxidase, as for the inhibition of neutrophil NAD(P)H oxidase, probability to reduce organ disorder by the disease that neutrophils such as inflammatory disease or circulatory disease or the like participated in was suggested (Schmid-SChonbe/n, G.W.et al, Physiology and pathology of leukocyte adherence, New York, OxfordUniversityPress, 1995).

On the other hand, that there was production ability of superoxide anion (02-) which was dependent on nADPH or NADH to smooth muscle cell, fibroblast, non phagocyte such as vascular endothelium cell or the like from previous was known, and cell function such as cell proliferation, hyperpermeability, contraction relaxation or the like and probability to be related to were pointed out (Grlendling, K.K.et al, Clrc. Res. 86,494-501,2000).

It was thought that the enzyme body was material same as neutrophil NAD(P) H oxidase at first.

It comprised in recent years, and gene of isozyme of gp91-pnox which was membrane constitution factor of neutrophil NAD(P) H oxidase was cloned in sequence.

Presently DuoX(dual oxidase) is reported as the isozyme which five kinds of Nox and peroxidase activities contain from Noxl to Nox5, too, too, and it becomes clear to form NoX-Duox family, and probability to participate in various tissue, expression of cell function and onset of disease is suggested (Lambeth, J.D, Curr. 0pin. Hematol. 9,11-17,2002).

As for vascular smooth muscle cell, NAD(P)H oxidase of vascular endothelium cell, participation is expected to various circulatory organ system disease from blood pressure regulation hormone such as angiotensin 11(Angll) or the like, cytokine, thrombin, PDGF, insulin, mechanical stimulation, hyperglycemia, activated case by many stimulations such as hyperlipidemia or the like.

Increase of 02-production with blood vessel wall through NAD(P)H oxidase is observed in hypertension rat model by spontaneous type hypertension rat model or Angll persistence administration or the like, and the case which it is increased, and is inhibited of blood pressure by inhibition of NAD(P)H oxidase is reported (Chen, X, et, al, Hypertenslon, 38,606-611,2001, Rey, F.E.b, Circ. Res. 89,408-414,2001).

This thing suggests the probability that NAD(P) H oXidase participates in blood pressure regulation.

Arteriosclerosis lesion is chronic inflammatory proliferation change of blood vessel, and ROS which is produced with blood vessel wall is carrying out important role in onset progress.

The case that arteriosclerosis lesion by hypercholesterol load is inhibited is reported in one p47phoX knock out mouse of cytoplasm Components of NAD(P)H oxidase (Stokes, K.Y.et al, CirC.ReS, 88,499-505,2001,Barry-Lane, P.A.et al, J.Clin. Invest. 108,1513-1522,2001).

ROS participates in proliferation of nascent intima produced after balloon disorder, and restenosis of blood vessel is caused.

Recently, that NAD(P)H oxidase activity is increased is reported in blood vessel wall after balloon

disorder (Shi, Y, et, al, Arterioscler. Thromb. Vasc.Biol. 21,739-745,2001, SzOCs, K, et, al, Arterioscler. Thromb. Vasc. Biol. 22,21-27,2002).

Moreover, the case that lowered activity of NAD(P)H oxidase by C242T gene mutation of one p22phox of cell membrane Components relates to lowering of coronary artery disease onset rate, too is reported (lnoue, N, et, al, Circulation, 97,135-137,1998, Cai, H, et, al, Eur. J.CIin. Invest-, 29,744-748,1999, Cahilly, C.b, CirC.Res. 86,391-395,2000).

These report suggests the probability that NAD(P) H oxidase participates in arteriosclerosis and onset progress of coronary artery disease.

As for ROS, probability to participate in onset progress of diabetes mellitus complication is pointed out.

What oxidation stress through NAD(P)H oxidse elevates in vascular endothelium cell by high sugar stimulation or stimulation of saccharification protein, smooth muscle cell or the like is reported (lnoguChi, T, et, al, Diabetes, 49,1939-1945, 2000, HinK, U, et, al, CirC.Res. 88, E14-E22,2001, Wautier, M, et, al, Am.J. Physiol-, 2.80, E685-B694,2001).

The case which disorder of rise and retina vascular endothelium cell of NAD(P)H oxidase activity relates to in retina blood vessel with diabetes mellitus model rat, too is reported (El1is, E.A.et al, Free Radic. Biol-Med. 24,111-120,1998).

The case which leukocyte participated in tissue disorder has been reported in cerebral circulation disorder such as cerebral apoplexy or the like (Hartl, R, et, al, J. Cereb. BIood Flow Metab. 16,1108-1119,1996).

The case that cerebral ischemia lesion is reduced is reported in the mouse that neutrophil NAD(P)H oxidase activity lacked (Walder, C.E.et al, Stroke, 28,2252-2258,1997).

Moreover, as for the ischemia, the inflammation, the stimulation such as for example beta-Amyloidor the like, probability to display neuron toxicity with case activating NAD(P)H oxidase of Microglia cell, too is reported (Spranger, M, et, al, J. Cereb. Blood Flow Metab. 18,674-678,1998, Vianca,V.D.). $, J.

Biol. Chem. 274,15493-15499, 1999, Green, S.P.et al, J. Cereb. Blood FlOWMetab. 21,374-384,2001).

These result suggests the probability that NAD(P) H oxidase participates in cerebral apoplexy and neurodegeneration disease.

Because ROS which is produced by NAD(P)H oxidase participates with cell proliferation and vascularization, relation of hyperplasia of tumor, too is suggested (Arnold, R.S.b, Proc. Natl. Acad. Scl. USA,98,5550-5555,2001=Arbiser, J.L.et al, ProC.Natl. Acad-Scl. USA,99,715-720,2002).

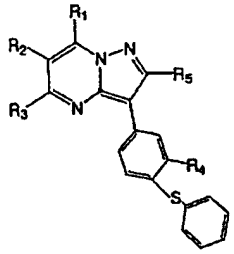
NAD(P) Hoxidase activity is reported with kidney, gastric mucosa cell, adipocyte, chondrocyte except that it was stated above, and relation of cell function is attracting attention.

In other words, a disease on the basis of inflammation, c irculatory disease, facilitation of proliferation activity is widely connected with NAD(P) H/oxidase to hypertension, diabetic complication, arteriosclerosis, coronary artery disease, cerebral apoplexy, ischemic disease, neurodegeneration disease, disturbance of pulmonary circulation, nephritis, arthritis, inflammatory disease and onset progress such as for example cancer or the like in aforesaid types.

There is a possibillity that, these diseases can be inhibited by NAD(P) H oxidase inhibitor.

Following one as compound containing pyrazolo [1,5-a] pyrimidine skeleton is common knowledge.

Tokkai 5-112571 discloses following compound

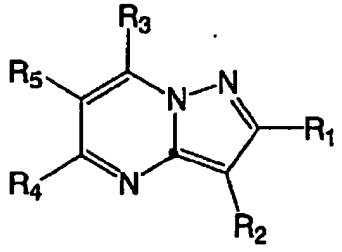


Wherein, R1 is hydrogen, OH.

R2 is hydrogen, lower alkoxycarbonyl, lower alkoxy, halogen, lower alkyl-CONHR6 (it is phenyl, lower alkyl with R6 containing hydrogen, halogen atom). R3 is hydrogen, OH, lower alkyl or the like. R5 is hydrogen, lower alkyl, lower alkoxy lower alkyl halogen lower alkyl and R4 is hydrogen, lower alkyl, lower alkoxy.

This compound hinders inhibition of androgen action expression, and, as applications, that treatment such as for example prostate gland hypertrophy, hirsutism of woman, male baldness, pimple and the like can be used is disclosed.

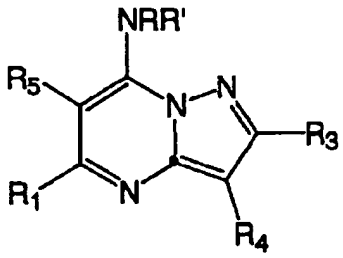
WOOO/59908 discloses following compound.



Wherein, R3 is (substituted) aryl, (substituted) heteroaryl, and R4 and R5 are hydrogen, halogen, CN, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, alkylthio, alkyl sulphinyl, alkyl sulphonyl, amino, alkylamino, (substituted) phenyl.

This compound has corticotropin releasing factor receptor antagonism, and, as applications, psychosis, nerve disease, anxiety, trauma stress, breast eclipse disorder, circulatory organ system disease and the like are nominated.

Tokkai 10-101672 discloses following compound.

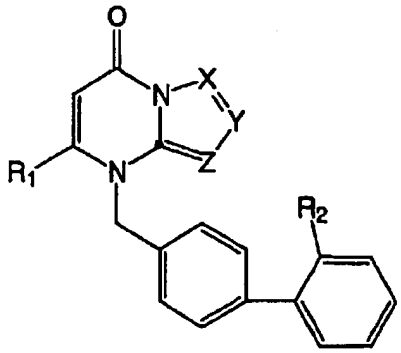


Wherein, R1 is hydrogen, (substituted) lower alkyl cycloalkyl, thienyl, furyl, lower alkenyl, (substituted) phenyl and R5 is hydrogen, lower alkyl.

This compound is used as adenosine promoter.

As applications, cardiac infarction, treatment of cerebral infarction are nominated.

Tokkai 7-157485 discloses following compound.



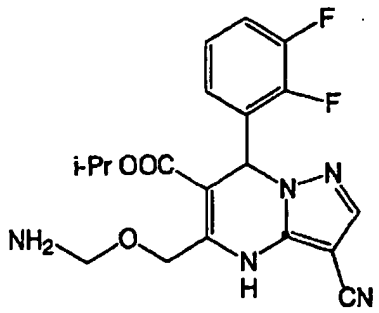
Wherein, R1 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower alkyl thio, and X, Y, Z is N, CR3.

This compound is angiotensin $ antagonist.

As applications, circulatory organ system disease, treatment of for example cerebral apoplexy are used

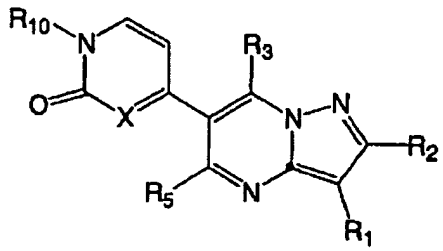
as.

EPO328700AI discloses following compound.



The treatment that cerebral circulation device damages this compound as applications is nominated.

WOOO/53605 discloses following compound.

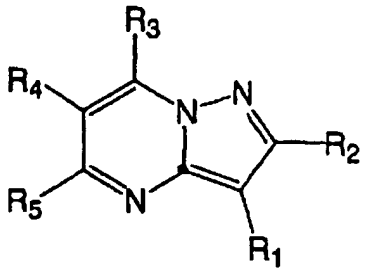


Wherein, X is CH, NR1. R3 is hydrogen, alkyl, alkenyl, alkynyl, aryl, halo, OH, heterocyclyl and R5 is hydrogen, alkyl, OH, 0-alkyl, halo, amino, nitro.

This compound has tyrosine kinase inhibitory action.

As applications, treatment such as for example cancer, vascularization, diabetes mellitus complication, inflammation or the like is nominated.

WO98/54093 discloses following compound.

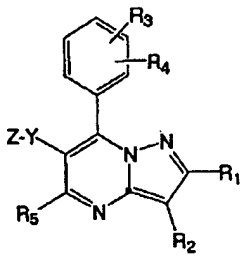


Wherein, R1 is hydrogen, (substituted) alkyl, cycloalkyl, aryl, (substituted) heterocyclyl, halo, OH, (substituted) heteroaryl, and R2 and R3 are hydrogen, alkyl, aryl, cycloalkyl, OH, halo, amino, nitro and R4 is hydrogen, (substituted) alkyl, cycloalkyl, alkoxy, (substituted) alkenyl, (substituted) alkynyl, (substituted) aryl, (substituted) heterocyclyl, alkoxy NRR, NO2, OH, NH2, (substituted) heteroaryl and R5 is hydrogen, alkyl, alkoxy, OH, halo, NO2, NH2.

This compound has tyrosine kinase inhibitory action.

As applications, cancer, vascularization, diabetes mellitus complication and inflammation treatment are nominated.

Tokkai 4-270285 discloses following compound.

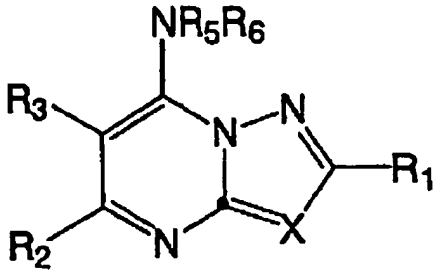


Wherein, Y is lower alkylene, lower alkenylene, and Z is substituted acetyl, heterocyclic or the like.

This compound hinders HMGCoA reductase.

As applications, treatment of hyperlipidemia is nominated.

WOOO/44754 discloses following compound.

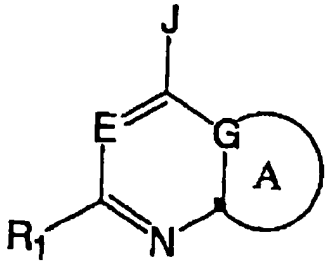


Wherein, as for R2 and R3, hydrogen, halogen, (substituted) alkyl, (substituted) alkenyl, (substituted) aryl, (substituted) aralkyl, (substituted) heterocyclic group or link together and are alkylene group, and X is N, CR4.

This compound inhibits fat accumulation.

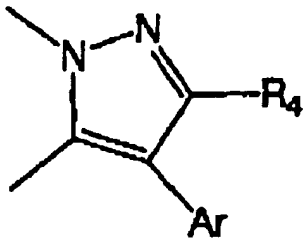
As applications, obesity, diabetes mellitus, hypertensive treatment are nominated.

Kokai 2000-383501 $, following compound are disclosed.



Wherein, E is N, CR9 (R9 is hydrogen, alkyl, halogen, cyanogen, hydroxy, alkoxy) and R1 is hydrogen, alkyl, cycloalkyl, alkoxy (alkyl), amino, aryl, heteroaryl.
J is NR2R3, OR, O, and G is C, N.

As heterocycle of A ring,

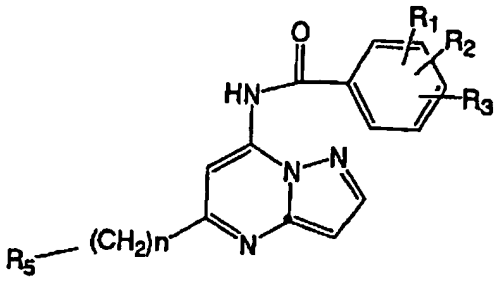


is nominated.

This compound has corticotropin releasing factor (CRF) receptor antagonism.

As applications, treatment of diabetes mellitus is nominated.

Tokkai 9-169762 discloses following compound.



Wherein, R5 is carboxy, lower alkoxy carboxy, (substituted) carbamoyl (phenyl lower alkyl lower alkyl substituent).
N is 1-5.

Function of this compound is vague.

As applications, use is nominated in analgesia, inflammation, antibacterial, hypoglycemic, cancer and the like.

Khim. -Farm. Zh (1995), 29 (4), 37-38 (2,5-dimethylpyrazolo [1,5-a] pyrimidine-7-yl) succinic acid is disclosed).

As applications, treatment of diabetes mellitus is nominated.

Problems to be Overcome by this Invention

This invention has the object of putting forward novel compound hindering NAD(P) H oxidase and a composition including compound thereof.

Moreover for example, this invention has the object of putting forward diagnostic agent diagnosing a disease to be related to NAD(P)H other than medicinal composition (quasi drug is included), animal drug (animal industry drug, veterinarian drug, fisheries drug or the like) composition.

In other words, by this invention being to put forward novel compound hindering NAD(P) H oxidase and a composition including compound thereof furthermore, a purpose is made that prevention or therapy makes hypertension, diabetic complication, arteriosclerosis, coronary artery disease, cerebral apoplexy, ischemic disease, neurodegeneration disease, disturbance of pulmonary circulation, nephritis, arthritis, inflammatory disease or cancer a disease on the basis of inflammation, circulatory disease, facilitation of proliferation activity.

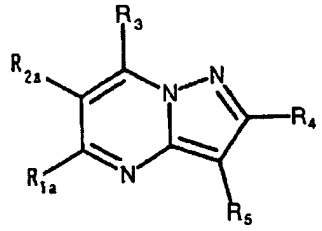
Gist of the invention.

That following pyrazolo [1,5-a] pyrimidine derivatives and analogs had NAD(P) H oxidase inhibitory action in neutrophil and blood vessel was discovered.

Active oxygen (ROS, superoxide) production is inhibited by hindering NAD(P)H oxidase, and various kinds of circulatory disease (hypertension, hyperlipidemia, diabetes mellitus, diabetic complication, arteriosclerosis, coronary artery disease, cerebral apoplexy, ischemic disease, neurodegeneration disease, disturbance of pulmonary circulation, cerebral circulation disorder, nephritis, arthritis, inflammatory disease or cancer or the like) and effect gastric mucosa disorder (example = gastric ulcer) are had.

In accordance with this invention following item 1-26 are been to put forward, and an aforesaid purpose is achieved.

1. Compound



(1a)

(wherein, R1a, R2a, R3-R5 each independently show hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted heterocyclic group, hydroxy, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted heterocyclic oxy, optionally substituted acyl, optionally substituted monosubstituted carbonyl oxy, optionally substituted carbamoyl, diazo, optionally substituted amidine, azide, two thoron, nitro, optionally substituted amino, optionally substituted imino, cyanogen, mercapto, optionally substituted monosubstituted thio, optionally substituted monosubstituted thio oxy, optionally substituted monosubstituted sulphinyl, optionally substituted monosubstituted sulfonyl, sulfo or tri substituted silyl, and R1a, R2a, R3-R5 each independently link together by an arbitrary combination, and it may be formed a ring structure). A prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. Wherein the following ten compounds are excluded.

(1).

Compound wherein, R1a is cycloalkyl, halogen lower alkyl or phenyl with hydrogen, OH, lower alkyl carbon number of 3-8.

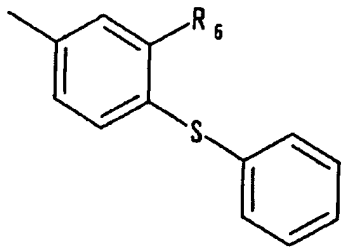
R2a hydrogen, lower alkoxycarbonyl, lower alkoxy, halogen, cycloalkyl of lower alkyl 3-8 C, lower alkoxycarbonyl lower alkyl carboxyl, carboxy lower alkyl-CONHR6 (is phenyl or lower alkyl with R6 containing hydrogen, halogen atom), cyanogen, phenyl with containing group selected from the group comprising hydroxy group, halogen atom, lower alkyl group, lower alkoxy and phenylthio group as

substituent, phenyl lower alkyl group with containing group selected from the group comprising hydroxy group and lower alkoxy group as substituent on the phenyl ring, lower alkanoyl group with containing lower alkanoyloxy lower alkyl, benzoyl group or halogen atom, or it is hydroxy lower alkyl group with containing group selected from the group comprising phenyl group and halogen atom as substituent.

R3 is hydrogen or OH.

R4 is hydrogen, lower alkyl, lower alkoxy lower alkyl or halogen lower alkyl.

R5 is



and R6 is hydrogen, lower alkyl or lower alkoxy.

(2).

Compound wherein, R1a, R2a are each independently hydrogen, halogen, CN, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, alkylthio, alkyl sulphinyl, alkyl sulphonyl, amino, alkylamino or (substituted) phenyls.

R3 is (substituted) aryl or (substituted) heteroaryl

(3).

Compound wherein, R1a is hydrogen, (substituted) lower alkyl cycloalkyl, thienyl, furyl, lower alkenyl or (substituted) phenyl

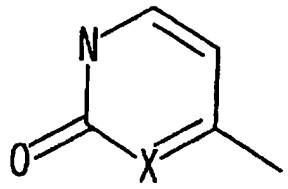
. R2a is hydrogen or lower alkyl.

R3 is optionally substituted amino.

(4).

Compound wherein, R1a is hydrogen, alkyl, OH, 0-alkyl, halo, amino or nitro.

R2a is



, and X is CH, N, and nitrogen atom on ring of R2a may be substituted.

R3 and R5 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, halo, OH, $ heterocyclyl.

(5).

Compound wherein, R1a is hydrogen, alkyl, alkoxy, OH, halo, NO2 or NH2.

R2a is hydrogen, (substituted) alkyl, cycloalkyl, alkoxy, (substituted) alkenyl, (substituted) alkynyl, (substituted) aryl, (substituted) heterocyclyl, alkoxy NRR, NO2, OH, NH2 or (substituted) heteroaryl.

R3 and R4 are each independently hydrogen, alkyl, aryl, cycloalkyl, OH, halo, amino, nitro.

R5 is hydrogen, (substituted) alkyl, cycloalkyl, aryl, (substituted) heterocyclyl, halo, OH or (substituted) heteroaryl.

(6).

Compound wherein, R2a is lower alkylene or lower alkenylene substituted by substituted acetyl or heterocycle.

R3 is optionally substituted phenyl.

(7).

Compound wherein, R1a, R2a are each independently hydrogen, halogen, (substituted) alkyl, (substituted) alkenyl, (substituted) aryl, (substituted) aralkyl, (substituted) heterocyclic group or alkylene groups same as.

R3 is optionally substituted amino

(8).

R1a is hydrogen, alkyl, cycloalkyl, alkoxy, -(alkyl) amino, aryl or heteroaryl.

R2a is hydrogen, alkyl, halogen, cyanogen, hydroxy or alkoxy.

R3 is optionally substituted amino or optionally substituted alkoxy.

R5 is aryl.

(9).

Compound wherein, R1a was substituted by group selected from the group comprising carboxy, lower alkoxy carboxy and substituted carbamoyl as substituent and is lower alkyl, and R2a is hydrogen.

R3 is phenyl carbonylamino, and the said phenyl group may be substituted.

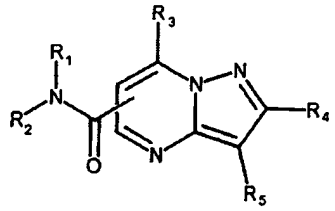
R4 and R5 are hydrogen.

(10).

(2,5-dimethylpyrazolo [1,5-a] pyrimidine-7-yl) succinic acid, wherein (the substituent which is not defined of among compound described in (1)-(10) denotes an arbitrary substituent).

2. Compound in accordance with Paragraph1 that one or both of R1a and R2a is hydrogen, and the other is optionally substituted carbamoyl.

3. Compound in accordance with Paragraph 1 represented by formula



(I)

a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. (wherein, R1 is hydrogen, lower alkyl optionally substituted amino or optionally substituted aryl lower alkyl and R2 are hydrogen, optionally substituted lower alkyl optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl optionally substituted aryloxy l, optionally substituted lower alkyl sulfonyl, optionally substituted aryl sulfonyl, optionally substituted heteroaryl lower alkyl optionally substituted heterocyclic group lower alkyl or optionally substituted amino.

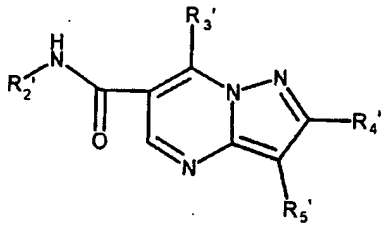
Or R1 and R2 comprises together with adjacent N atom, and optionally substituted heterocycle may be formed.

R3 is hydrogen, hydroxy, lower alkoxy, halogen or optionally substituted amino.

R4 is hydrogen, lower alkyl or optionally substituted aryl.

R5 is hydroxy, optionally substituted lower alkyl optionally substituted aryl, optionally substituted aryl

lower alkyl optionally substituted cycloalkyl lower alkyl, optionally substituted aryl lower alkenyl, optionally substituted cycloalkyl lower alkenyl, optionally s, optionally substituted cycloalkyl lower alkynyl, optionally substituted aryl carbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted heterocyclic group, halogen, CH0, optionally substituted amino or optionally substituted imino. But wherein compounds of following formula are excluded



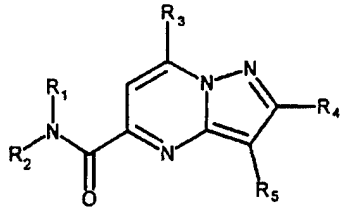
(I')

(wherein, R2' is the phenyl which may be substituted by hydrogen, lower alkyl or halogen, and R3 'is hydrogen or hydroxy.

R4 'is hydrogen or lower alkyl.

R5 'contains phenylthio group, and is the phenyl which may substitute by lower alkyl or lower alkoxy furthermore).

4. Compound in accordance with Paragraph3 represented by formula



(I-1)

(same meaning the aforesaid each substituent), a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein.

5. Compound described in paragraph3 or 4 &. A prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. R1 is hydrogen.

R2 is optionally substituted aryl.

6. Compound, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof

wherein are described in paragraph3 or 4 &. R3 is hydrogen or the amino which may be substituted.

7. Compound, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein are described in paragraph3 or 4 &. R4 is hydrogen.

8. Compound, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein are described in paragraph3 or 4) . R5 is optionally substituted aryl.

9. Compound, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein are described in paragraph3 or 4 &. R1 is hydrogen and R2 is optionally substituted phenyl.
R3 is hydrogen or the amino which may be substituted and R4 is hydrogen.
R5 is optionally substituted phenyl.

10. Compound in accordance with Paragraph9, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. Substituent is at least one which is selected from the group which comprised optionally substituted heterocyclic group, lower alkyl carbonyl, cycloalkyl, lower alkyl optionally substituted amino, halogen, halogenation lower alkyl, lower alkoxy, carboxy lower alkyl oxy, heterocyclic group lower alkyl oxy, amino lower $$$, hydroxy, cyanogen, carbamoyl heterocyclic group oxy, cyano lower alkyl and phenyl in the phenyl which may be substituted of R2.

11. Compound in accordance with Paragraph10, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. R2 is optionally susbstituted heterocyclic group phenyl.

12. Compound in accordance with Paragraph10, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. R2 is optionally substituted piperazino phenyl, optionally substituted piperidino phenyl or the pyrrolidino phenyl which may be substituted.

13. Compound in accordance with Paragraph9 which is at least one which is selected from the group that substituent comprised halogen, halogenation lower alkyl, aryl lower alkyl oxy, lower alkyl, lower alkoxy, hydroxy, lower alkyl thio, phenyl, phenyloxy, phenyl lower alkyl, phenyl lower alkyl amino, phenyl lower alkyl thio, phenyl lower alkenyl, phenylcarbamoyl, amino, cycloalkyl lower alkyl oxy and

heteroaryl lower alkyl oxy in the phenyl which R5 might substitute, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein.

14. Compound in accordance with any of Paragraph1-13 is contained and is medicinal composition.

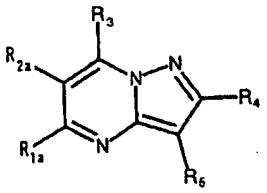
15. Compound in accordance with any of Paragraph1-13 is contained and is NAD(P) H oxidase inhibitor.

16. Preventative agent of disease compound in accordance with any of Paragraph1-13 is contained, and to be related to NAD(P) H or therapeutic agent.

17. Preventative agent or therapeutic agent in accordance with Paragraph16 which is selected from the group which a the aforesaid disease damaged inflammation, disturbance of pulmonary circulation, ischemic cardiac disease, cerebral circulation, and comprised arteriosclerosis, diabetes mellitus complication, hypertension and proliferation associated disease.

18. Preventative agent or therapeutic agent in accordance with Paragraph16 that a the aforesaid disease is cerebral infarction or diabetic retinopathy.

19. Compound represented by

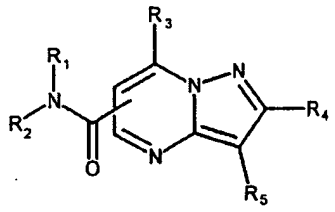


(Ia)

, prodrug thereof, pharmaceutically permitted salt thereof or solventate thereof is contained and is NAD(P)H oxidase inhibitor. (wherein, R1a, R2a, R3-R5 each independently show hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted heterocyclic group, hydroxy, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted heterocyclic oxy, optionally substituted acyl, optionally substituted monosubstituted carbonyl oxy, optionally substituted carbamoyl,

diazo, optionally substituted amidine, azide, two thoron, nitro, optionally substituted amino, optionally substituted imino, cyanogen, mercapto, optionally substituted monosubstituted thio, optionally substituted monosubstituted thio oxy, optionally substituted monosubstituted sulphinyl, optionally substituted monosubstituted sulfonyl, sulfo or tri substituted silyl, and R1a, R2a, R3-R5 each independently link together by an arbitrary combination, and it may be formed a ring structure).

20. Compound represented by



(I)

, prodrug thereof, pharmaceutically permitted salt thereof or solventate thereof is contained and is NAD(P)H oxidase inhibitor. (wherein, R1 is hydrogen, lower alkyl optionally substituted amino or optionally substituted aryl lower alkyl and R2 are hydrogen, optionally substituted lower alkyl optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl optionally substituted aryloxy l, optionally substituted lower alkyl sulfonyl, optionally substituted aryl sulfonyl, optionally substituted heteroaryl lower alkyl optionally substituted heterocyclic group lower alkyl or optionally substituted amino.

Or R1 and R2 comprises together with adjacent N atom, and optionally substituted heterocycle may be formed.

R3 is hydrogen, hydroxy, lower alkoxy, halogen or optionally substituted amino.

R4 is hydrogen, lower alkyl or optionally substituted aryl.

R5 is hydroxy, optionally substituted lower alkyl optionally substituted aryl, optionally substituted aryl lower alkyl optionally substituted cycloalkyl lower alkyl, optionally substituted aryl lower alkenyl, optionally substituted cycloalkyl lower alkenyl, optionally s, optionally substituted cycloalkyl lower alkynyl, optionally substituted aryl carbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted heterocyclic group, halogen, CH0, optionally substituted amino or optionally substituted imino.

21. Process for the therapy or prevention of disease it is characterised in that, and to be related to NAD(P) H to administer effective dose of compound in accordance with any of Paragraph1-20 to animal including human being.

22. Process in accordance with Paragraph21. Wherein, a the aforesaid disease is selected from the group which comprised inflammation, disturbance of pulmonary circulation, ischemic cardiac disease, Masaru circulatory disease, arteriosclerosis, diabetes mellitus complication, hypertension and proliferation associated disease.

23. Process in accordance with Paragraph21 that a the aforesaid disease is cerebral infarction or diabetic retinopathy.

24. Use of compound in accordance with any of Paragraph1-20 to produce pharmaceutical to be used in order to do prevention or therapy of a disease to be related to NAD(P) H.

25. Use in accordance with Paragraph24. Wherein, a the aforesaid disease is selected from the group which comprised inflammation, disturbance of pulmonary circulation, ischemic D disease, cerebral circulation disorder, arteriosclerosis, diabetes mellitus complication, hypertension and proliferation associated disease.

26. Use in accordance with Paragraph24 that a the aforesaid disease is cerebral infarction or diabetic retinopathy.

Detailed Description of the Invention

These inventors were discovered the compound which contained the aforesaid skeleton which had NAD(P) H inhibitory action as a result of having continued effort assiduously.

As for the term which is used in this specification, it should be understandable to be used with the definition to be used in an aforesaid sphere usually so long as it is not in particular mentioned.

In this specification, as "alkyl" used singly or in combination with other terms, branched or straight

chain c1-C20 alkyl is included.

For example, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, 1-butyl, t-butyl, n-pentyl, 1-ethyl propyl, 2-methyl butyl, 3-methyl butyl, 2,2-dimethyl propyl, n-hexyl, 2-methyl pentyl, 3-methyl pentyl, 4-methyl pentyl, n-heptyl, 2-methyl hexyl, 3-methyl hexyl, 4-methyl hexyl, 5-methyl hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, tetrahydrogeranyl, n-dodecyl, n-tri decyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-octadecyl, n-nonadecyl and n-eicosanyl are nominated.

Preferably CI to C9 alkyl is nominated.

More preferably CI to C6 alkyl, in particular preferably C1-C4 alkyl are nominated.

As the embodiment which substituent is desirable for in "optionally substituted alkyl", halogen, hydroxy, optionally substituted lower alkoxy, optionally substituted aryloxy, optionally substituted substituted carbonyl oxy, optionally substituted carbamoyl, diazo, cyanogen, optionally substituted amino, optionally substituted imino, optionally substituted amidine, azide, nitro, two thoron, mercapto, optionally substituted monosubstituted thio, optionally substituted monosubstituted thio oxy, optionally substituted monosubstituted sulphinyl, optionally substituted monosubstituted sulfonyl, sulfo, optionally substituted saturated or unsaturated alicyclic hydrocarbon group, optionally substituted aryl, optionally substituted heterocyclic group, optionally substituted heterocyclic oxy, optionally substituted acyl and tri substituted silyl and the like are nominated.

Moreover, in this specification, it states with carbon number in group thereof being 1-10, preferably1-8, more preferably 1-6, more particularly preferably 1-4 various group "is lower".

In this specification, number of substituents to substitute hydrogen in alkyl group in "optionally substituted alkyl" is 1-5, preferably 1-3.

Position of substituent is not restricted in particular.

In this specification, as "optionally substituted alkenyl", branched or straight chain c2 to CI2 alkenyl is

included.

These can contain double bond the possible number that can be located in, and configuration can be recovered (E) configuration or (Z) configuration in their double bond, but for example vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl, geranyl, 1-decenyl, 1-tetra decenyl, 1-octadecenyl, 9-octadecenyl, 1-eicosenyl, 3,7,11,15-tetramethyl-1-hexadecenyl and the like is included.

Preferably C2 to C8 alkenyl is nominated.

More preferably C2 to C6 alkenyl is nominated.

Wherein vinyl in particular, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-methyl-2-butenyl are preferred.

In this specification, as "optionally substituted", aforesaid "is the top and similar as in case of called "alkyl" which may substitute".

In this specification, number of substituents is 1-5, preferably 1-3 in "optionally substituted alkenyl".

Position of substituent is not restricted in particular.

In this specification, as "optionally substituted alkynyl", branched or straight chain c2 to CI2 alkynyl is included.

It is possible that these contain triple bond the possible number that can be located in, but alkynyl group and the like which may contain for example ethinyl, 1-propynyl, 2-propynyl (propargyl), carbon number 2 to 20 double bond such as for example 2-butenyl, 2-pentene-4-ynyl and the like are nominated.

Preferably C2 to C8 alkynyl is nominated.

More preferably C2 to C6 alkynyl is nominated.

In this specification, as "optionally substituted", it is similar as in case of "alkyl" named aforesaid "optionally substituted".

In this specification, number of substituents is 1-5, preferably 1-3 in "optionally substituted alkynyl".

Position of substituent is not restricted in particular.

It is halogen, hydroxy, lower alkoxy, lower alkenyloxy and acyl group that is preferred in the aforesaid substituent.

In this specification, acyl group and the like to be derived from the optionally substituted carboxylic acid, optionally substituted hydroxycarboxylic acid as "optionally substituted acyl" is nominated.

In an embodiment, group and the like represented with formula R6C(O)-, R70C(O)- (wherein, R6 and R7 each independently denote optionally substituted hydrocarbon group or heterocyclic group) is nominated.

Preferably it is group represented by formula R6C(O)-.

In this specification, it is As in "hydrocarbon group or the heterocyclic group which may be substituted" represented by R6 and R7, "hydrocarbon group", alicyclic hydrocarbon group which branched or straight chain aliphatic hydrocarbon group (alkyl, alkenyl, alkynyl group or the like) and the like are nominated as acyclic group, and is saturated or unsaturated as cyclic group moiety (cycloalkyl, cycloalkenyl, cycloalka dienyl group or the like), aryl group and the like are nominated.

In this specification, for example, as preferred embodiment of "acyl", formyl, acetyl, propionyl, butyryl,

isobutyryl, valeryl, 1-6C alkanoyl such as for example isovaleryl, pivaloyl, hexanoyl and the like, benzoyl, 2,4-dihydroxyphenyl carbonyl, 2,4-dihydroxy-3-(3-methyl-2-butenyl) phenyl carbonyl and the like are nominated.

As "optionally substituted", it is similar as in case of "alkyl" named aforesaid "optionally substituted".

Number of substituents to substitute hydrogen in acyl group in "optionally substituted acyl" is 1-5, preferably 1-3.

Position of substituent is not restricted in particular.

Moreover, as preferred example of "optionally substituted acyl", optionally substituted acetyl, optionally substituted benzoyl group are nominated, wherein as substituent and site of substitution substituting benzene ring hydrogen of benzoyl group, for example 2-, 3-, or 4-fluoro, 2-, 3-, or 4-chloro, 2-, 3-, or 4-bromo, 2-, 3-, or 4-iodo, 2-, 3-, or 4-methyl, 2,3-, 2,4- or 2,5-dimethyl, 2,6-, 3,4- or 3,5-dimethyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6- or 3,4,5-trimethyl, 2-, 3-, or 4-ethyl, 2-, 3-, or 4-propyl, 2-, 3-, or 4-trifluoromethyl, 2-, 3-, or 4-methoxy, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxy, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6- or 3,4,5-trimethoxy, 2-, 3-, or 4-ethoxy, 2-, 3-, or 4-propoxy, 2-, 3-, or 4-trifluoromethoxy, 2-, 3-, or 4-cyanogen, 2-, 3-, or 4-nitro.
And the combination that is these substituents and arbitrary possible of site of substitution is nominated.

In this specification, as "tri substituted silyl", it states with radical substituted onto hydrogen of 3 of silyl (-SiH3).

Tri substituted silyl may be substituted preferably. It is dialkyl silyl, dialkyl monoaryl silyl or mono alkyl diaryl silyl.

As embodying example of trialkylsilyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl are nominated.

As example of mono alkyl diaryl silyl, t-butyl diphenyl silyl or the like is nominated.

In this specification, as aliphatic hydrocarbon group of the "aliphatic hydrocarbon group which may be substituted", it states with branched or straight chain aliphatic hydrocarbon group (alkyl, alkenyl, alkynyl group or the like).

In this specification, as "halogen", for example, fluorine, chlorine, bromine, iodine are nominated.

As "optionally substituted", it is similar as in case of "alkyl" named aforesaid "optionally substituted".

In this specification, for example, as "optionally substituted alkoxy", "lower alkoxy", "lower alkenyloxy" and the like are nominated.

In this specification, as "lower alkoxy", lower alkyl thereof is same as the aforesaid definition. However, for example, alkoxy of carbon number 1 to 6 such as for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso butoxy, neo butoxy, t-butoxy, pentoxy, iso pentoxy and the like are nominated.

As "optionally substituted", it is similar as in case of "alkyl" named aforesaid "optionally substituted".

In this specification, as "lower alkenyloxy", lower alkenyl thereof is same as the aforesaid definition. However, for example, vinyloxy, allyloxy, 1-propenyl oxy, 2-methyl-1-propenyl oxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 2-ethyl-1-butenyloxy, 3-methyl-2-butenyloxy, 1-pentenyl oxy, 2-pentenyl oxy, 3-pentenyl oxy, 4-pentenyl oxy, 2-7C alkenyloxy such as for example 4-methyl-3-pentenyl oxy and the like are nominated.

As "optionally substituted", it is similar as in case of "alkyl" named aforesaid "optionally substituted".

In this specification, as "aryloxy", in embodiments, group and the like represented with formula R80- (wherein, R8 is same as the definition of "optionally substituted aryl") is nominated.

For example, phenoxy and the like are nominated.

In this specification, in an embodiment, as the "monosubstituted carbonyl oxy which may be substituted,

group and the like represented with formula R9C(O)0-, R10OC(O)0- (wherein, R9 and R10 are same as the definition of optionally substituted acyl") is nominated.

For example, alkyl carbonyl oxy, cycloalkyl carbonyl oxy, aryl carbonyl oxy, heterocyclic carbonyl oxy and the like are nominated.

In this specification, as "alkyl carbonyl oxy", for example, methyl carbonyl oxy, ethyl carbonyl oxy, propyl carbonyl oxy, isopropyl carbonyl oxy, butyl carbonyl oxy, isobutyl carbonyl oxy, t-butyl carbonyl oxy, pentyl carbonyl oxy, isopentyl carbonyl oxy, neopentyl carbonyl oxy, t-pentyl carbonyl oxy, $, 2-7C alkyl carbonyl oxy such as for example xyl carbonyl oxy and the like are nominated.

As "optionally substituted", it is similar as in case of "alkyl" named aforesaid "optionally substituted".

In this specification, as "optionally substituted carbamoyl", it is formula R11R12NC(= 0)-. (wherein, R11 and R12 hydrogen, optionally substituted lower alkyl optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy lower alkyl, optionally substituted lower alkyl sulfonyl, optionally substituted aryl sulfonyl, optionally substituted heteroaryl lower alkyl, optionally substituted heterocyclic group lower alkyl, optionally substituted amino). Group and the like represented with] which may form the heterocycle which $ R and R12 comprise together with adjacent N atom, and may be substituted is nominated.

As "optionally substituted carbamoyl", in an embodiment for example, carbamoyl, N-mono lower alkyl carbamoyl, N,N-dilower alkyl carbamoyl, N-hydroxy carbamoyl, N-lower alkoxy carbamoyl, N-hydroxy-N-lower alkyl carbamoyl, N-lower alkoxy-N-lower alkyl carbamoyl, N-phenylcarbamoyl, N-substituted phenylcarbamoyl group and the like are nominated.

As "optionally substituted", it is similar as in case of "alkyl" named aforesaid "optionally substituted".

As the aforesaid "N-mono lower alkyl carbamoyl", lower alkyl thereof is same as the aforesaid definition. However, for example, N-methylcarbamoyl, N-ethyl carbamoyl, N-propyl carbamoyl, N-

isopropyl carbamoyl, N-pentyl carbamoyl, N-iso pentyl carbamoyl, N-neopentyl carbamoyl, N-t-pentyl carbamoyl, N-1-ethyl propyl carbamoyl, N-hexylcarbamoyl and the like are nominated.

As the aforesaid "N,N-dilower alkyl carbamoyl", lower alkyl thereof is same as the aforesaid definition. However, for example, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-propyl carbamoyl, N-butyl-N-methylcarbamoyl, N-butyl-N-ethyl carbamoyl, N-butyl-N-propyl carbamoyl, N-butyl-N-isopropyl carbamoyl, N,N-dibutyl carbamoyl, N-ethyl-N-propyl carbamoyl, N,N-dipropyl carbamoyl, N-isopropyl-N-n-propyl carbamoyl, N-isopropyl-N-methylcarbamoyl and the like are nominated.

As the aforesaid "N-hydroxy-N-lower alkyl carbamoyl", lower alkyl thereof is same as the aforesaid definition. However, for example, N-hydroxy-N-methylcarbamoyl, N-hydroxy-N-ethyl carbamoyl, N-hydroxy-N-propyl carbamoyl, N-hydroxy-N-butyl carbamoyl, N-hydroxy-N-isopropyl carbamoyl, N-hydroxy-N-isobutyl carbamoyl, N-hydroxy one N-sec-butyl carbamoyl, N-hydroxy-N-t-butyl carbamoyl, N-hydroxy-N-pentyl carbamoyl, N-hydroxy-N-iso pentyl carbamoyl, N-hydroxy-N-lower alkyl carbamoyl group of carbon number 2-7 such as for example N-hydroxy-N-neopentyl carbamoyl and the like are nominated.

As the aforesaid "N-lower alkoxy-N-lower alkyl carbamoyl". Lower alkyl thereof is same as the aforesaid definition, n-lower alkoxy one N-lower alkyl carbamoyl that total carbon number thereof is 3 to 13, for example N-methoxy-N-methylcarbamoyl, N-methoxy-N-ethyl carbamoyl, N-methoxy-N-propyl carbamoyl, N-methoxy-N-butyl carbamoyl, N-methoxy-N-isopropyl carbamoyl, N-methoxy-N-isobutyl carbamoyl, N-methoxy-N-sec-butyl carbamoyl, N-methoxy-N-t-butyl carbamoyl, N-methoxy-N-pentyl carbamoyl, N-methoxy-N-iso pentyl carbamoyl, N-methoxy-N-neopentyl carbamoyl and the like are nominated.

As substituent of the aforesaid "N-substituted phenylcarbamoyl", lower alkyl, lower alkoxy, hydroxy and the like are nominated, and those meanings are similar to the aforesaid definition. However, for example, as preferred embodiment of "N-substituted phenylcarbamoyl", (4-methylphenyl) carbamoyl, (4-ethylphenyl) carbamoyl, (4-hydroxyphenyl) carbamoyl, (4-methoxyphenyl) carbamoyl (2,3-dihydroxyphenyl), carbamoyl (2,3-methoxyphenyl), carbamoyl (2,4-dihydroxyphenyl), carbamoyl,

(2,4-methoxyphenyl) carbamoyl (2,6-dihydroxyphenyl), carbamoyl (2,6-methoxyphenyl), carbamoyl (2,4,6-trihydroxyphenyl), carbamoyl (2,4,6-trimethoxyphenyl), carbamoyl (2,4-dimethoxy-6-hydroxyphenyl), carbamoyl (2,6-dimethoxy-4-hydroxyphenyl), ca, (4,6-dihydroxy-2-methoxyphenyl) carbamoyl (2,6-dihydroxy-4-methoxyphenyl), carbamoyl (2,3,4-trimethoxyphenyl), carbamoyl (2,3-dimethoxy-4-hydroxyphenyl), carbamoyl (2,4-dimethoxy-3-hydroxyphenyl), carbamoyl (2,3-dihydroxy-4-methoxyphenyl), (2,4-dihydroxy-3-methoxyphenyl) carbamoyl (2,4-dimethoxy-6-methylphenyl), carbamoyl (2,6-dimethoxy-4-methylphenyl), carbamoyl and the like are nominated.

In this specification, for example, as "optionally substituted amino", amino, mono lower alkyl amino, dilower alkyl amino, lower alkyl carbonylamino group, lower alkoxycarbonyl lower alkyl amino, hydroxy lower alkyl amino, carbamoyl amino, lower alkoxy lower alkyl amino, lower alkyl sulfonyl amino, cycloalkyl amino and the like are nominated.

As "optionally substituted", it is similar as in case of "alkyl" named aforesaid "optionally substituted".

Said substituent comprises together with N atom of amino, and heterocycle may be formed.

As the aforesaid "mono lower alkyl amino", lower alkyl thereof is same as the aforesaid definition. However, for example, methylamino, ethylamino, propylamino, isopropyl-amino, butyl amino, isobutyl amino, sec-butylamino, t-butylamino, carbon number 1-6 mono lower alkyl amino group such as for example pentyl amino, isopentyl amino, hexyl amino and the like are nominated.

As the aforesaid "dilower alkyl amino". Di lower alkyl amino that lower alkyl thereof is same as the aforesaid definition, and total carbon number thereof is 2-20, for example dimethylamino, ethylmethyl amino, diethylamino, methylpropyl amino, ethyl propylamino, isopropyl methylamino, isopropyl ethylamino, butyl methylamino, butyl ethylamino, in butyl methylamino, in butyl ethylamino and the like are nominated.

As the aforesaid "lower alkyl carbonylamino", lower alkyl thereof is same as the aforesaid definition. However, for example, alkyl carbonylamino radical of carbon number 2 to 7 such as for example methyl carbonylamino, ethyl carbonylamino, propyl carbonylamino, isopropyl carbonylamino, butyl

carbonylamino, isobutyl carbonylamino, sec-butyl carbonylamino, t-butyl carbonylamino, pentyl carbonylamino, isopentyl carbonylamino and the like are nominated.

In this specification, as "imino", it states with R13-NH-CR14 group or CR15 = NH radical, and wherein, R13-R15 means hydrogen, aforesaid "alkyl", "aralkyl", "acyl", optionally substituted aryl sulfonyl (for example alkyloxyphenyl sulfonyl) alkylsulfonyl, carbamoyl and the like.

In this specification, hydroxy, alkoxy, "alkyl", "aralkyl", "acyl", optionally substituted aryl sulfonyl (for example alkyloxyphenyl sulfonyl) alkylsulfonyl, carbamoyl and the like are nominated as example of substituent in "optionally substituted imino".

For example, "optionally substituted imino", imino, hydroxyimino (oxime), methylimino, ethyl imino, dimethyl imino, benzyl imino, benzoyloxy imino, benzoyl imino, acetylimino, propionyl imino, tert butoxy carbonyl imino, methylsulfonyl imino, 4-methoxyphenyl sulfonyl imino and the like are nominated.

Imino in particular, methylimino, dimethyl imino, diethyl imino, acetylimino are preferred.

In this specification, as "optionally substituted amidino", it states with-C(=NH)NH2 radical, and substituent is similar to it in case of "alkyl" named aforesaid "optionally substituted" in "optionally substituted amidino", and nitrogen atom of an any may be substituted.

In this specification, for example, as the "saturated or unsaturated alicyclic hydrocarbon group which may be substituted", cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalka dienyl and the like are nominated.

As example of the aforesaid cycloalkyl group, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2-2.1] heptyl, bicyclo[2.2.2] octyl, bicyclo[3.2.1] octyl, bicyclo[3.2.2] nonyl, bicyclo[3.3.1] nonyl, bicyclo[4.2.1] nonyl, 3-20C cycloalkyl group and the like such as for example bicyclo[4.3.1] decyl, adamantyl and the like are nominated.

As example of the aforesaid cycloalkenyl group, for example, and cycloalkenyl group and the like of 4-

20C is nominated such as 2-cyclopentyl-1-yl, 3-cyclopenten-1-yl , 2-cyclohexen-1-yl , carbon number such as for example 3-cyclohexen-1-yl and the like.

As example of the aforesaid cycloalka dienyl group, for example, cycloalka dienyl group and the like of 4-20C is nominated such as 2,4-cyclopentadien-1-yl , 2,4-cyclohexa dien-1-yl , carbon number such as for example 2,5-cyclohexa dien-1-yl and the like.

In this specification, for example, as "optionally substituted aryl", 6-20C aryl group and the like such as for example phenyl, indenyl, naphthyl, (1-naphthyl, 2-naphthyl and the like), anthryl, phenanthryl, acenaphthylenyl, fluorenyl (9-fluorenyl, 1-fluorenyl and the like) or the like is nominated.

(substituted). Aryl includes both of unsubstituted aryl and substituted aryl.

2-, 3-, or 4-fluoro wherein, for example as substituent and site of substitution of benzene ring of "optionally substituted phenyl", 2-, 3-, or 4-bromo = 2-, 3-, or 4-chloro, 2-, 3-, or 4-iodo, 2-, 3-, or 4-methyl, 2,3-, 2,4- or 2,5-dimethyl, 2,6-, 3,4- or 3,5-dimethyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6- or 3,4,5-trimethyl.
The combination that is substituent of 2-, 3-, or 4-ethyl, 2-, 3-, or 4-propyl, 2-, 3-, or 4-trifluoromethyl, 2,3-= 2-, 3-, or 4-methoxy, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxy, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6- or 3,4,5-trimethoxy, 2-, 3-, or 4-ethoxy, 2-, 3-, or 4-propoxy, 2-, 3-, or 4-trifluoromethoxy, 2-, 3-, or 4-cyanogen, 2-, 3-, or 4-nitro and these and arbitrary possible of site of substitution is nominated.

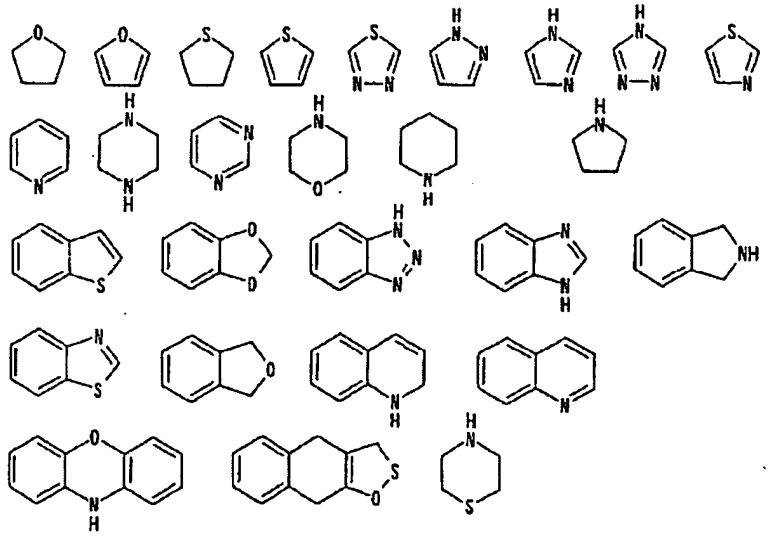
In this specification, aromatic fused heterocycle group or non aromatic monocyclic heterocyclic group and the like which oxygen, sulfur, heterocyclic group containing 1 heteroatom at least of nitrogen are meant as atom constituting ring system as heterocyclic group of "the heterocyclic group which may be substituted", and have tricyclic characteristics or for example aromatic monocyclic heterocyclic group, 2 bamboo blind is nominated.

As embodiment of monocyclic heterocyclic group thereof, for example, furyl, thienyl, pyronyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl,

furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, quinolyl, piperazinyl, piperidinyl, pyrrolidinyl and the like are nominated.

Moreover, for example, as embodiment of aromatic fused heterocycle group having dicyclic or tricyclic characteristics thereof, benzofuranyl, the isobenzofuranyl, benzo (b) thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzo isoxazolyl, benzothiazolyl, 1,2-benzo isothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnonyl, quinazolinyl, quinoxalinyl, phthalidinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, alpha-carbolinyl, beta-carbolinyl, gamma-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathienyl, thianthrenyl, phenathridinyl (sic), phenathrolinyl (sic), indolizinyl, pyrrolo (1,2-b) pyridazinyl, pyrazolo (1,5-a) pyridyl, imidazo (1,2-a) pyridyl, imidazo (1,5-a) pyridyl, imidazo (1,2-b) pyridazinyl, imidazo (1,2-a) pyrimidinyl, 1,2,4-triazolo (4,3-a) pyridyl, 1,2,4-triazolo (4,3-a) pyridazinyl and the like are nominated.

Below, as preferred heterocyclic group, examples comprise compounds of formula wherein one of the hydrogens is missing.



Wherein, it is the arbitrary position which is chemically possible, and deficiency position of hydrogen obtains it, and there may be it on aromatic ring, and there may be it on non aromatic ring.

More preferably, it is 5-7 membered N atom containing non-aromatic ring and for example, is piperazinyl, piperidinyl or pyrrolidinyl.

In this specification, in an embodiment, as the "heterocyclic oxy which may be substituted", group and the like represented with formula R160- (wherein, R16 denotes optionally substituted heterocyclic group) is nominated.

As the aforesaid "saturated or unsaturated alicyclic hydrocarbon group which may be substituted", "optionally substituted aryl", preferred example of substituent of "the heterocyclic group which may be substituted", for example optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, halogen, hydroxy, optionally substituted lower alkoxy, optionally substituted aryloxy, optionally substituted monosubstituted carbonyl oxy, optionally substituted carbamoyl, diazo, cyanogen, optionally substituted amino, optionally substituted imino, optionally substituted amidine, azide, nitro, two thoron, mercapto, optionally substituted monosubstituted thio, optionally substituted monosubstituted thio oxy, optionally substituted monosubstituted sulphinyl, optionally substituted substituted sulfonyl, sulfo, optionally substituted saturated or unsaturated alicyclic hydrocarbon group, optionally substituted aryl, optionally substituted heterocyclic group, optionally substituted heterocyclic oxy, optionally substituted acyl and tri substituted silyl and the like are nominated.

If there is substituent, number thereof is 1-3, preferably 1.

Position of substituent is not restricted in particular.

It is lower alkyl substituted by hydroxy, lower alkyl, lower alkoxy, lower alkenyloxy, lower alkyl carbonyl oxy or hydroxy, lower alkoxy or lower alkyl carbonyl group that is preferred in the aforesaid substituent.

Is aforesaid ||, as "preferred example of lower alkyl carbonyl j, lower alkyl thereof is the aforesaid definition and identical". However, for example, acetyl, propionyl, butyryl, isobutyryl, valeryl, 2-6C

alkanoyl group such as for example isovaleryl, pivaloyl, hexanoyl and the like are nominated.

As preferred example of the aforesaid "lower alkoxycarbonyl", lower alkoxy thereof is the aforesaid definition and identical. However, for example, methoxycarbonyl, ethoxycarbonyl, n-propoxy carbonyl, 2-7C alkoxycarbonyl group such as for example n-butoxy carbonyl and the like are nominated.

It is just what the roller was described as term of substituent of the "aliphatic hydrocarbon group which might be substituted" when it was meant of substituent except it.

In this specification, in an embodiment, as the "monosubstituted thio which may be substituted", group and the like represented with formula R17S- (wherein, R17 denotes optionally substituted hydrocarbon group or heterocyclic group) is nominated.

As ideal "??? thio", for example, monosubstituted thio group of carbon number 1-6 such as for example methylthio, ethylthio, propylthio, isopropylthio, butyl thio, isobutyl thio, neo butyl thio, t-butylthio, pentyl thio, hexyl thio and the like are nominated.

In this specification, in an embodiment, as the "monosubstituted thio oxy which may be substituted", group and the like represented with formula R18SO- (wherein, R18 denotes optionally substituted hydrocarbon group or heterocyclic group) is nominated.

In this specification, in an embodiment, as the "monosubstituted sulfonic acid which may be substituted", group and the like represented with formula R19S(O)2- (wherein, R19 denotes optionally substituted hydrocarbon group or heterocyclic group) is nominated.

In an embodiment, as the "monosubstituted sulphinic acid which may be substituted", group and the like represented with formula R20S(O)- (wherein, R20 denotes optionally substituted hydrocarbon group or heterocyclic group) is nominated.

In this specification, it is As in "hydrocarbon group or the heterocyclic group which may be substituted" represented by R17-R20, "hydrocarbon group", alicyclic hydrocarbon group which branched or straight

chain aliphatic hydrocarbon group (alkyl, alkenyl, alkynyl group or the like) and the like are nominated as acyclic group, and is saturated or unsaturated as cyclic group moiety (cycloalkyl, cycloalkenyl, cycloalka dienyl group or the like), aryl group and the like are nominated.

The one which is same it was exemplified in the aliphatic hydrocarbon group which might make monosubstituted as example of alkyl, alkenyl, alkynyl group of the aforesaid "hydrocarbon group" is nominated.

The one which is same it was exemplified in substituent of the "aliphatic hydrocarbon group which might be substituted" as example of cycloalkyl, cycloalkenyl, cycloalka dienyl group of the aforesaid "hydrocarbon group" is nominated.

As example of aryl group of the aforesaid "hydrocarbon group", for example, 6-20C aryl group and the like such as for example phenyl, indenyl, naphthyl, (1-naphthyl, 2-naphthyl and the like), anthryl, phenanthryl, acenaphthylenyl, fluorenyl (9-fluorenyl, 1-fluorenyl and the like) or the like is nominated.

Oxygen, sulfur, aromatic fused heterocycle group and the like which heterocyclic group containing 1 heteroatom is meant and is preferably at least heteroaromatic ring group, and have for example aromatic monocyclic heterocyclic group, dicyclic or tricyclic characteristics of nitrogen are nominated as atom constituting ring system as "heterocyclic group" in the aforesaid "hydrocarbon group or heterocyclic group which may be substituted".

As embodiment of monocyclic heterocyclic group thereof, for example, furyl, thienyl, pyronyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, quinolyl and the like are nominated.

Moreover, for example, as embodiment of aromatic fused heterocycle group having dicyclic or tricyclic characteristics thereof, benzofuranyl, the isobenzofuranyl, benzo (b) thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzo isoxazolyl, benzothiazolyl, 1,2-benzo isothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnonyl, quinazolinyl, quinoxalinyl, phthalidinyl,

naphthyridinyl, purinyl, pteridinyl, carbazolyl, alpha-carbolinyl, beta-carbolinyl, gamma-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathienyl, thianthrenyl, phenathridinyl (sic), phenathrolinyl (sic), indolizinyl, pyrrolo (1,2-b) pyridazinyl, pyrazolo (1,5-a) pyridyl, imidazo (1,2-a) pyridyl, imidazo (1,5-a) pyridyl, imidazo (1,2-b) pyridazinyl, imidazo (1,2/ a) pyrimidinyl, 1,2,4-triazolo (4,3-a) pyridyl, 1,2,4-triazolo (4,3-a) pyridazinyl and the like are nominated.

Wherein heterocyclic group containing only oxygen atom as ring system atom, for example furyl, benzo (b) furyl, 2H m pyran-3-yl, isobenzofuran, 2H-chromen-3-yl , xanthenyl, chromanyl, isochromanyl, 2H-$ mouth (3,2-b) pyran, cyclopenta (b) pyran, 2H-benzopyranyl and the like are more preferred.

As substituent of the aforesaid "hydrocarbon group or heterocyclic group which may be substituted", the "saturated or unsaturated alicyclic hydrocarbon group which may be substituted" which is substituent of the "aliphatic hydrocarbon group which may be substituted", "optionally substituted aryl" and group same as substituent of "the heterocyclic group which may be substituted" are nominated.

As preferred embodiment of the "aliphatic hydrocarbon group which may be substituted", for example, in addition to the following in particular preferred embodiment, isopentenyl, 2-hydroxy-3-methyl-butyl, 3-hydroxy-2-phenylpropyl, 3-(2,4-dihydroxyphenyl carbonyl) butyl, 2-methoxy-3-methyl-butyl, 3-methoxy-2-phenylpropyl, 2-(2-butenyloxy)-3-methyl-butyl, 3-(2,4-dihydroxyphenyl) propyl, 3-(2,4-dimethoxyphenyl carbonyl) butyl, 2-hydroxy-butyl, 2-hydroxy-3-methyl-pentyl, 2-methoxy-butyl, 2-methoxy-3-methyl-pentyl and the like are nominated.

As in particular preferred embodiment of the "aliphatic hydrocarbon group which may be substituted", for example, methyl, ethyl, n-propyl, 1-propyl, n-butyl, 1-butyl, n-pentyl, 3-methyl butyl, 2,2-dimethyl propyl, n-hexyl, 3-methyl butyl, 4-methyl pentyl, n-heptyl, n-octyl, n-nonyl, tetrahydrogeranyl, n-decyl, n-pentadecyl, trifluoromethyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 4-pentenyl, geranyl, 2-propynyl ($$$$$$), 2-butenyl and the like are nominated.

In this specification, "notation" (*) shows presence of asymmetric carbon, and the R body which is stereoisomer, S body or any of mixture thereof is shown.

In the compound of this invention, various stereoisomer can be present, but both thereof are contained in $ compound of this invention.

Moreover, when geometric isomer is present, it may be any of cis or trans.

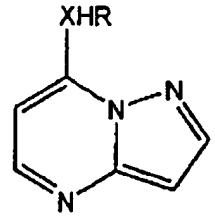
In this specification, hydroxy, Me are carbinyl, and ethyl, 1-Pr are isopropyl, and TBS is tertm butyldimethylsilyl, and, as for H, as for hydrogen, OH, as for Et, SEM denotes 2-(trimethylsilyl) ethoxymethyl.

Bzl is benzil, and Me is carbinyl, and Ph is phenyl, and MOM is methoxymethyl, and TMS is trimethylsilyl, and straight chain hexyloxy, Ts are p-toluenesulfonyl, and TBDPS is tert-butyl diphenyl silyl, and But is tert-butyl, and iPr is isopropyl, and, as for prenyl, as for prenyl group (3-methyl-2-butenyl group), prenyloxy, as for prenyl oxy, "OC6H, one c", as for cyclohexyl oxy, "OC6H, 1-n", plcolyloxy denotes picoryl oxy.

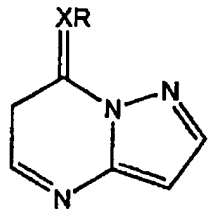
Moreover. "2" shows that is disubstituted.

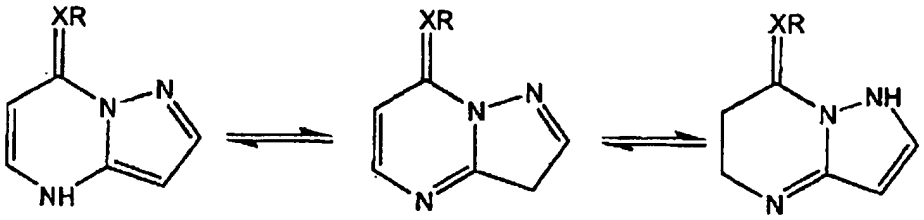
(substituted). (substituted) is used in alkyl, (substituted) aryl or the like in order to show both of unsubstituted although functional group thereof is substituted.

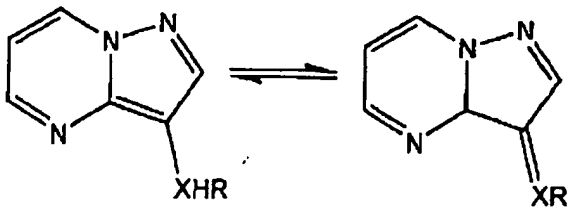
Compound containing alpha hydrogen to substituent of this invention contains following tautomer.



X denotes O or N.
When X is O, R is not present.
When X is N, R is an arbitrary substituent.







These tautomers are contained in this invention.

Compounds of this invention (la) is preferably compound (1) and is more preferably compound (1-1).

In compound (la),R1a is preferably optionally substituted carbamoyl and is more preferably CONRIR2.

R2a is preferably hydrogen.

In compound (la), when R1a, R2a, R3-R5 link together by an each arbitrary combination, and ring structure is formed, said ring includes the preferably aforesaid heterocycle which may be substituted and optionally substituted hydrocarbon ring and is 5-7 membered ring.

When the Practical Embodiment of 1 of this invention was shown with aforesaid formulae (1), R1 is hydrogen.
R2 is optionally substituted aryl.
R3 is hydrogen or the amino which may be substituted and R4 is hydrogen.
R5 is the compound which is optionally substituted aryl.

When the preferred Practical Embodiment of this invention was shown with aforesaid formulae (1), R1 is hydrogen.
It is the aryl which R2 may be substituted by substituent more than 1 or 2 which is selected from the group which comprised optionally substituted heterocyclic group, lower alkyl carbonyl, cycloalkyl, lower alkyl optionally substituted amino and phenyl.
R3 is hydrogen or the amino which may be substituted and R4 is hydrogen.
R5 is the compound which is the aryl which may be substituted by the substituent which is selected from the group which comprised halogen, halogenation lower alkyl, aryl lower alkyl oxy, lower alkyl, lower alkoxy, hydroxy, lower alkyl thio, phenyl, phenyloxy, phenyl lower alkyl, phenyl lower alkyl oxy, phenyl lower alkyl amino, phenyl lower alkyl thio, phenyl lower alkenyl, phenylcarbamoyl, amino, cycloalkyl lower alkyl oxy and heteroaryl lower alkyl oxy.

When the more preferred Practical Embodiment of this invention was shown with aforesaid formulae (1), it is comprise the following. R1 is hydrogen.

R2 is phenyl substituted by substituent more than 1 or 2 which was selected from the group which comprised optionally substituted heterocyclic group, lower alkyl carbonyl, cycloalkyl, lower alkyl optionally substituted amino and phenyl.

R3 is hydrogen or the amino which may be substituted and R4 is hydrogen.

R5 is phenyl substituted by the substituent which was selected from the group which comprised halogen, halogenation lower alkyl, aryl lower alkyl oxy, lower alkyl, lower alkoxy, hydroxy, lower alkyl thio, phenyl, phenyloxy, phenyl lower alkyl, phenyl lower alkyl amino, phenyl lower alkyl thio, phenyl lower alkenyl, phenylcarbamoyl, amino, cycloalkyl lower alkyl oxy and heteroaryl lower alkyl oxy.

In the aforesaid Practical Embodiment,R2 is preferably phenyl substituted by optionally substituted heterocyclic group and is more preferably phenyl substituted by optionally substituted 5-7 membered N atom containing non-aromatic aliphatic heterocyclic group (example = piperazine, piperidine, pyrrolidino) .

In this case, substituent of "optionally substituted" can be present in arbitrary position on heterocyclic and/or phenyl.

In R3 (,). Substituent is lower alkylene which preferably heteroatom may exist among (example =-CH_2-CH_2-CH_2-CH_2-, -CH_2-CH_2-CO-CH_2-CH_2-), mono or dilower alkyl optionally substituted phenyl in optionally substituted amino (substituent = halogen and the like).

When the more preferred Practical Embodiment of this invention was shown with aforesaid formulae (1). A compound wherein, R1 is hydrogen.

R2 is selected from the group which comprised optionally substituted 2-, 3- and 4-piperazino phenyl, optionally substituted 2-, 3- and 4-pyrrolidino phenyl and optionally substituted 2-, 3- and 4-piperidino phenyl and R3 is hydrogen and R4 is hydrogen.

R5 is phenyl substituted by the substituent which was selected from the group which comprised halogen, halogenation lower alkyl lower alkyl, lower alkoxy, hydroxy, lower alkyl thio, phenyl, phenyloxy, phenyl lower alkyl, phenyl lower alkyl oxy, phenyl lower alkyl amino, phenyl lower alkyl thio, phenyl

lower alkenyl, phenylcarbamoyl, amino, cycloalkyl lower alkyl oxy and heteroaryl lower alkyl oxy.

As "salt" of the target compound of this invention, the salt which is pharmacologically acceptable is preferred, and salt of for example inorganic base, salt of organic base, salt of inorganic acid, salt of organic acid, basicity or or the like of acidic amino salt is nominated.

As salt of inorganic base, alkali metal salt such as sodium salt, potassium salt or the like, alkaline earth metal salt such as calcium salt, magnesium salt, barium salt or the like and aluminium salt, ammonium salt or the like are nominated.

As salt of organic base, salt such as trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N, N'-dibenzylethylenediamine or the like is nominated.

As salt of inorganic acid, salt such as hydrochloric acid, hydrofluoric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, perchloric acid, hydroiodic acid or the like is nominated.

As salt of organic acid, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, mandelic acid, ascorbic acid, lactic acid, gluconic acid, methanesulfonic acid, salt such as p-toluenesulfonic acid, benzenesulfonic acid or the like are nominated.

As salt of basic amino acid, salt such as arginine, lysine, ornithine or the like is nominated, and, as salt of acidic amino acid, salt such as aspartic acid, glutamic acid or the like is nominated.

The compound of this invention containing one or more chiral center can exist as optically active substance.

In the same way said compound alkenyl or alkenylene being including it, cis and probability of trans isomer are present.

Mixture of R- and S-isomer including R- and S-isomer, mixture and racemic mixture of cis and trans isomer is included by range of this invention.

Asymmetric carbon atom can be present with substituent such as alkyl group.

All the such isomers are included in the same way as in mixtures thereof in this invention.

When specific stereoisomer is desired, it is produced using process to separate using well known method after starting material containing asymmetric center separated beforehand is produced using well known method to a person skilled in the art submitting to it to stereospecific reaction or being produced mixture of stereoisomer.

Prodrug is the compound which it is derivative of compound having NAD(P) H oxidase inhibiting activity to contain chemical or the group which can be metabolically decomposed, and comprise pharmacologically active compound in in-vivo under physiological condition by solvolysis.

Derivative of said compound has activity in both of acid derivative or base derivative. However, acid derivative is useful in solubility, tissue connectivity, release regulation in hoof milk species life (Bungard, H, Design of Prodrugs, pp. 7-9,21-24,Elsevler, Amsterdaml985).

For example, prodrug including acidic derivative such as amide to be produced because the acidic compound which is comprised and ester to be produced by reacting suitable alcohol react acidic compound and the suitable amine that it is been made into, too is well-known to a person skilled in the art.

Ester of aromatic is preferred prodrug whether it is the aliphatic which is simple derivitised from the acidic group which said compound is containing.

More preferably it is C1-C6 alkyl ester (for example methyl ester, ethyl ester, n-propyl ester, isopropylester, n-butyl ester, isobutyl ester, tert-butyl ester) morpholinoethyl ester and N,N-diethyl glycol amide ester of acidic group.

The prodrug which is methyl ester can be produced by the reaction of the sodium salt of compound represented by for example general formula (la) with methyl iodide (can be acquired from Aldrich Chemical Co, Milwaukee, Wisconsin USA; product number No. 28, 956-6) (in solvent such as for example dimethylformamide and the like).

The prodrug which is ethyl ester can be produced by the reaction of the sodium salt of compound represented by for example general formula (la) with ethyl iodide (can be acquired from Aldrich Chemical Co, Milwaukee, Wisconsin USA; product number No.1-778-O) (in solvent such as for example dimethylformamide and the like).

The prodrug which is N,N-diethyl glycol amide ester can be produced by the reaction of the sodium salt of compound represented by general formula (la) with 2-chloro-N,N-diethylacetamide (can be acquired from Aldrich Chemical Co, Milwaukee, Wisconsin USA; product number No. 25, 099-6) (in solvent such as for example dimethylformamide and the like).

The prodrug which is he morpholinoethyl ester can be produced by the reaction of the sodium salt of compound represented by general formula (la) with 4-(2-chloroethyl) morpholine hydrochloride (can be acquired from Aldrich Chemical CO, Milwaukee, Wisconsln USA; product number No.C4,220-3) (in solvent such as for example dimethylformamide and the like).

Depending on the situation, a double ester form prodrug such as (acyl oxy) alkyl ester or ((alkoxycarbonyl)oxy) alkyl ester can be produced.

In this specification, the comprising term which "pharmacologically acceptable" is mixed with other component in formulation, and that it is not adverse is meant for recipient.

As "solventate" of the target compound of this invention, hydrate and alcohol ?? are exemplified, and hydrate is preferred, and moreover hydrate salt is included, and in an embodiment monohydrate, dihydrate, hexahydrate and the like are nominated.

As composition, medicinal composition (quasi drug is included), animal drug (animal industry drug, veterinarian drug, fisheries drug or the like) composition and the like are nominated.

In other words, in a person and animal, as NAD(P)H inhibitor, or it is useful as diagnostic agent checking a disease to be related to NAD(P) H.

In the disease that it can be dealt using a composition of this invention, inflammation, disturbance of pulmonary circulation, ischemic cardiac disease (for example coronary artery disease) menses circulatory disease (for example brain edema, cerebral infarction) arteriosclerosis (for example atherosclerosis) diabetes mellitus complication, hypertension, proliferation associated disease and the like are nominated.

General preparation method of medicinal composition below of this invention is shown.

The compound of this invention combines it with carrier permitted by pharmacological, and administration can be carried out orally or aorally as solid formulation such as for example tablet, encapsulated formulation, granule, powder, dusting powder, bougie or liquid formulation such as for example syrup, injection, suspending agent, solvent, spray agent.

As pharmacologically permitted carrier, solvent, solubilizer, suspending agent, isotonizing agent, buffer agent, analgesic and the like are nominated in liquid formulation excipient, lubricant, binding agent, disintegrating agent, collapse inhibitor, absorption accelerating agent, adsorbent, lagging material, solubilizer, stabilising agent in solid formulation.

Moreover. $ can be used.

And a composition of this invention can be formulated substance containing NAD(P) H inhibition except this invention.

As administration pathway of aoral, intravenous injection, intramuscular injection, transnasal, $$,-oma and percutaneous and the like are nominated.

In solid formulation, as excipient, for example, glucose, lactose, sucrose, D-mannitol, crystalline cellulose, starch, calcium carbonate, light anhydrous silicic acid, sodium chloride, kaolin and urea and the like are nominated.

In solid formulation, as lubricant, for example, magnesium stearate, calcium stearate, boric acid powder, colloidal silicic acid, talc and polyethyleneglycol and the like are nominated.

In solid formulation, as binding agent, for example, water, ethanol, propanol, refined sugar, D-mannitol, crystalline cellulose, dextrin, methyl cellulose, hydroxypropylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose, starch solution, gelatin solution, polyvinylpyrrolidone, calcium phosphate, potassium phosphate and shellac and the like are nominated.

In solid formulation, as disintegrating agent, for example, starch, carboxymethylcellulose, carboxymethylcellulose calcium, agar powder, end of lamina orchid, crosscarmellose sodium, carboxymethyl starch sodium, sodium alginate, sodium bicarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid ester species, sodium lauryl sulfate, starch, stearic acid monoglyceride, lactose and calcium carboxymethyl cellulose and the like are nominated.

As ideal example of inhibitor collapsing in solid formulation, hydrogenation oil, $$, stearin, cacao butter and hardened oil and the like are nominated.

In solid formulation, as absorption accelerating agent, for example, quaternary ammonium salt group species and sodium lauryl sulfate and the like are nominated.

In solid formulation, as adsorbent, for example, starch, lactose, kaolin, bentonite and colloidal silicic acid and the like are nominated.

In solid formulation, as lagging material, for example, glycerol, starch and the like are nominated.

In solid formulation, as solubilizer, for example, arginine, glutamic acid, aspartic acid and the like are nominated.

In solid formulation, as stabilising agent, for example, human serum albumin, lactose and the like are nominated.

It may be coated with tablet, when preparing pill or the like, film of in accordance with requirements stomach or enteric canal soluble substance (refined sugar, gelatin, hydroxypropylcellulose, hydroxypropyl methyl cellulose phthalate and the like) as solid formulation.

To tablet, the tablet which was carried out ordinary agent coating in accordance with requirements, for example sugar coated tablet, gelatin encapsulation tablet, $$$$, film coatings tablet or double tablet, multilayer tablet are included.

Hard capsule and soft capsule are included to encapsulated formulation.

When, above-mentioned to form to a form of a bougie can be added for example higher alcohol, esters of higher alcohol, semi-synthetic glyceride and the like besides listed additive.

In liquid formulation as ideal example of solvent, water used for injection, alcohol, propylene glycol, macrogol, sesame oil and maize oil and the like are nominated.

In liquid formulation as ideal example of solubilizer, polyethyleneglycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, Tris aminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate and the like are nominated.

In liquid formulation as ideal example of suspending agent, detergent such as for example stearyl triethanolamine, sodium lauryl sulfate, lauryl amino propionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate and the like, hydrophilic macromolecule and the like such as for example for example polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxyethyl cellulose, hydroxypropylcellulose and the like are nominated.

In liquid formulation as ideal example of isotonizing agent, sodium chloride, glycerol, D-mannitol and the like are nominated.

In liquid formulation as ideal example of buffer agent, buffer and the like such as for example phosphate, acetate, carbonate and citrate or the like is nominated.

In liquid formulation as ideal example of bad malignant transformation medicine, benzyl alcohol, benzalkonium chloride and procaine hydrochloride and the like are nominated.

In liquid formulation as ideal example of preservatives, parahydroxybenzoic acid esters, chlorobutanol, benzyl alcohol, 2-phenylethyl alcohol, dehydroacetic acid, $$$$ acid and the like are nominated.

In liquid formulation as ideal example of anti-oxidant, sulfite, ascorbic acid, alpha-tocopherol and cysteine and the like are nominated.

It is preferred when, liquid agent and the suspending agent which are prepared as injection are sterilized and to be isotonic with blood.

Usually these are sterilised by filtration using bacteria retaining filter and the like, compound of fungicide or irradiation.

After these treatments, solid is formed using process such as for example lyophilization or the like furthermore, and use immediately beforehand sterile water or sterile injectable diluent (hydrochloric acid lidocaine aqueous solution, physiological saline, dextrose aqueous solution, ethanol or mixed solution or the like of these) may be added.

Moreover, $ $, medicinal composition may include other agent to the dwarf who is L coloring agent, preservative, flavor, taste and flavouring agents, edulcorant if they are requirements.

In this specification, that medicinal composition including as compound of this invention or it is combined and administered with other therapeutic agent with alone is meant "if [subj] administer".

For example, it is separate, but, as for the combination, ors simultaneously simultaneously run side by side as mixture.
It can be administered with a thing of $ consecutively $.

Including and combined agent are separates, but moreover the procedure that it is been simultaneously (case through the vein line which for example, is separate to equal individual) administered includes the presentation which this is alike in the agent which was made to grapple together as therapy mixture, and is $$$, too.

Firstly "combination" administration is given, and continuing that it administers to separate by 1 of compound or agent given to 2 is included furthermore.

In this specification, as "administers NAD(P)H oxidase inhibitor before a sign of disease to be related to NAD(P)H is found". For example, that NAD(P) H oxidase inhibitor is administered as above to anterior than a point in time that condition of disease to be related to aforesaid such that NAD(P)H or a sign is confirmed by diagnosis of medical doctor or each patient is aware of is meant.

In this specification, as "hypertension", there is meant associated disease requiring administration in mammal by acceleration properties hypertension, suprarenal hypertension, benign hypertension, borderline type hypertension, essential hypertension, ????? hypertension, idiopathy hypertension, labile hypertension, bad hypertension, $$$ hypertension, ??????????????, post partum hypertension, primary hypertension, pulmonary hypertension, renal hypertension, renovascular hypertension, secondary hypertension, curative effective amount of the compound represented by general formula (la) of sufficient amount though or systemic venous hypertension or NAD(P)H oxidase is hindered.

In this specification, as "diabetic complication", there is meant associated disease requiring administration to mammalian organisms by curative effective amount of compound represented by general formula (la) of sufficient amount, to hinder diabetic nephropathy, diabetic $$$$$$, or diabetic retinopathy or NAD(P)H oxidase.

In this specification, as "arteriosclerosis", there is meant associated disease requiring administration to mammalian organisms by coronary artery hardening, hypertrophic arteriosclerosis, hypertensive arteriosclerosis, artery tunica media hardening, $$$$$$ arteriosclerosis, nodosity arteriosclerosis, occlusive arteriosclerosis, peripheral arteriosclerosis, curative effective amount of the compound represented by general formula (la) of sufficient amount though or senile arteriosclerosis or NAD(P)H oxidase is hindered.

In this specification, as "coronary artery disease", there is meant associated disease requiring administration to mammalian organisms by curative effective amount of the compound represented by general formula (la) of sufficient amount though angina pectoris, coronary artery cancer, coronary artery hardening, coronary artery thrombosis, coronary artery vasospasm, cardiac infarction, or myocardium stun or NAD(P)H oxidase is hindered.

In this specification, as "cerebral apoplexy", there is meant associated disease requiring administration in mammal by curative effective amount of the compound represented by general formula (la) of sufficient amount though bleeding in hypertensive brain, cerebral infarction, transient ischemia attack, or spider submembranous bleeding or NAD(P)H oxidase is hindered.

In this specification, as an "ischemic disease" , there is meant associated disease requiring administration to mammalian organisms by curative effective amount of the compound represented by general formula (la) of sufficient amount though cardiac infarction, or attack or NAD(P)H oxidase is hindered.

In this specification, as "neurodegeneration is damaged", there is meant associated disease requiring administration to mammalian organisms by curative effective amount of the compound represented by general formula (la) of sufficient amount though disease or NAD(P)H oxidase related to before Alzheimer's disease, Parkinson's disease, the amyotrophic side bare sclerosis, pigmented retinitis, cerebellum modified brain tumor, or is hindered.

In this specification, with "disturbance of pulmonary circulation", there is meant associated disease requiring administration to anterior milk animal by curative effective amount of the compound represented by general formula (la) of sufficient amount though pulmonary artery thrombus, embolism,

pulmonary edema, pulmonary hypertension, or chronic cor pulmonale or NAD(P)H oxidase is hindered.

In this specification, as "nephritis", there is meant associated disease requiring administration to crest milk animal by immune complex glomerulonephritis, glomerulonephritis, immunity relation glomerulonephritis (for example proliferative glomerulonephritis) chronic glomerulonephritis, curative effective amount of the compound represented by general formula (la) of sufficient amount though or proliferative glomerulonephritis or NAD(P)H oxidase is hindered.

In this specification, as "arthritis", there is meant associated disease requiring administration to mammalian organisms by curative effective amount of the compound represented by general formula (la) of sufficient amount though acute rheumatic arthritis, chronic rheumatism, Chlamydia arthritis, chronic absorbable arthritis, chyle arthritis, arthritis on the basis of bowel disease, filarial arthritis, $$$ arthritis, $$$ arthritis, $$$$ arthritis, hypertrophic arthritis, juvenile arthritis, juvenile chronic arthritis, lime arthritis, neonatal arthritis of foals, nodosity arthritis, ochronotic arthritis, psoriatic arthritis, or pyogenic arthritis or NAD(P)H oxidase is hindered.

In this specification, as an "inflammatory disease", there is meant associated disease requiring administration in mammals by curative effective amount of the compound represented by general formula (la) of sufficient amount though inflammatory enteric disease, septicemia, septicemia shock, adult respiration distress syndrome, pancreatitis are hindered. Shock caused by trauma. bronchial asthma, allergic rhinitis, rheumatoid arthritis, chronic rheumatism, arteriosclerosis, bleeding in brain, cerebral infarction, cardiac failure, cardiac infarction symptom, psoriasis, $$$$$$, cerebral apoplexy, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, arthrosis deformans, gout, myelitis, ankylosing spondylitis, $$$$ syndrome, psoriasis arthropathy, spondylitis, young person arthropathy or young person ankylosing spondylitis, reactive arthropathy, infectivity arthritis or arthritis after infection, gonococcal arthritis, tuberculous arthropathy, viral arthritis, arthritis by fungus, syphilitic arthritis, Lyme disease, arthritis caused by "vasculitis syndrome". Is used repeated ly species-itis (tennis elbow), carpal tunnel syndrome in port of nodosity polyarteritis, hypersensitivity vasculitis, Luegenec granulomatosis, polymyalgia rheumatism, articulation cell rheumatism, calcium crystal precipitation arthropathy, false draft, non-$$$ rheumatism, synovial fluid vane-itis, thigh waist-itis disorder (typing), mixed form of arthritis, neuropathic arthropathy disease, hemorrhagic arthropathy,

vascular peliosis, hypertrophic osteoarthrosis, $$$$$$$$$. Arthritis caused by a specific disease, hemoglobin composed-sis, falciform erythrocyte disease and other hemoglobinopathy, high ribo protein-emia, hypo $$$$$$$-emia, parathyroid gland hyperfunction, acromegaly, familial the ground sea disaster, Behat disease, systemic autoimmune disease rouge are $$, disease such as or relapsing polychondritis or NAD(P)H oxidases.

In this specification, with "cancer", there is meant associated disease requiring administration in mammal by curative effective amount of the compound represented by general formula (la) of sufficient amount to hinder carcinoma (for example $$$$, mucus sarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, $$$, angiosarcoma, endothelium sarcoma, lymph duct sarcoma, lymph duct endothelioma, periosteum-oma, mesothelioma, $$$$$ tumor, leiomyosarcoma, rhabdomyosarcom or NAD(P)H oxidase.

(for example lipozome, fine particle, microcapsule or the like) which is able to be used in order various deliveries system is common knowledge and to administer the compound of this invention.

As introduction process, intracutaneous, intramuscular, intravenous in peritoneal cavity, subcutaneous, epidural in nasal cavity and oral pathway are proposed, but it is not restricted to these.

In the compound or the composition, it can be been administered by the pathway which is arbitrary convenient (for example, it is passed through epithelium or layer in mucosa, and, by injection or bolus injection, $ is absorbed) and it can be been administered together with other biologically inert agent.

It is systemic or topical, and administration is obtained.

Moreover, the pathway which is arbitrary appropriate at a composition or pharmacological compound of this invention (injection in cerebral ventricle and injection in pith cavity are included).
For example, as for the injection in cerebral ventricle, it can be expected what is introduced into central nervous system using) which it can be readily done using catheter in menses ventricle added fitting in to a reservoir such as 0mmaya reservoir.

For example, moreover, by formulation using inhalator or use and aerosolize agent of nebulizer, lung administration can be used, too.

Dose of the compound of this invention differs by age of $$$, body weight, symptom or administration method or the like, and it is not restricted in particular. However, it is 0.01mg-log and it is 0.1 mg-1 g, 1 mg-100 mg, 0.1 mg-10 mg and is preferably obtained usually per adult per day if oral administration is carried out.

In case of parenteral administration, it is 0.01 mg-1 g and it is 0.01 mg-100 mg, 0.1 mg-100 mg, 1 mg-100 mg, 0.1 mg-10 mg and is preferably obtained.

(Ideal form for Carrying Out the Invention.

It is possible that or salts thereof or solventate thereof is readily produced using itself a well-known method.

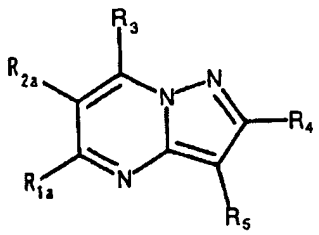
As embodiment of said process, for example following process for the production or method based on this is nominated.

As preparation method of compound (la), preparation method of compound (1) is exemplified.

It can be composed from the amine which is following compound A and arbitrary appropriate the compound of this invention containing in formula (1).

Patent Claims

1. Compound



(Ia)

(wherein, R1a, R2a, R3-R5 each independently show hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted heterocyclic group, hydroxy, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted heterocyclic oxy, optionally substituted acyl, optionally substituted monosubstituted carbonyl oxy, optionally substituted carbamoyl, diazo, optionally substituted amidine, azide, two thoron, nitro, optionally substituted amino, optionally substituted imino, cyanogen, mercapto, optionally substituted monosubstituted thio, optionally substituted monosubstituted thio oxy, optionally substituted monosubstituted sulphinyl, optionally substituted monosubstituted sulfonyl, sulfo or tri substituted silyl, and R1a, R2a, R3-R5 each independently link together by an arbitrary combination, and it may be formed a ring structure). A prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. Wherein the following ten compounds are excluded.

(1)

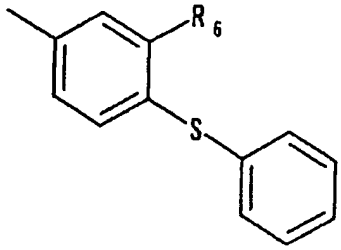
Compound wherein, R1a is cycloalkyl, halogen lower alkyl or phenyl with hydrogen, OH, lower alkyl carbon number of 3-8.

R2a hydrogen, lower alkoxycarbonyl, lower alkoxy, halogen, cycloalkyl of lower alkyl 3-8 C, lower alkoxycarbonyl lower alkyl carboxyl, carboxy lower alkyl-CONHR6 (is phenyl or lower alkyl with R6 containing hydrogen, halogen atom), cyanogen, phenyl with containing group selected from the group comprising hydroxy group, halogen atom, lower alkyl group, lower alkoxy and phenylthio group as substituent, phenyl lower alkyl group with containing group selected from the group comprising hydroxy group and lower alkoxy group as substituent on the phenyl ring, lower alkanoyl group with containing lower alkanoyloxy lower alkyl, benzoyl group or halogen atom, or it is hydroxy lower alkyl group with containing group selected from the group comprising phenyl group and halogen atom as substituent.

R3 is hydrogen or OH.

R4 is hydrogen, lower alkyl, lower alkoxy lower alkyl or halogen lower alkyl.

R5 is



and R6 is hydrogen, lower alkyl or lower alkoxy.

(2).

Compound wherein, R1a, R2a are each independently hydrogen, halogen, CN, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, alkylthio, alkyl sulphinyl, alkyl sulphonyl, amino, alkylamino or (substituted) phenyls.

R3 is (substituted) aryl or (substituted) heteroaryl

(3).

Compound wherein, R1a is hydrogen, (substituted) lower alkyl cycloalkyl, thienyl, furyl, lower alkenyl or (substituted) phenyl

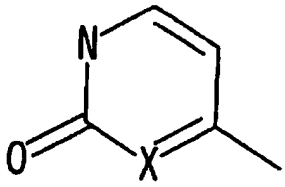
. R2a is hydrogen or lower alkyl.

R3 is optionally substituted amino.

(4).

Compound wherein, R1a is hydrogen, alkyl, OH, 0-alkyl, halo, amino or nitro.

R2a is



, and X is CH, N, and nitrogen atom on ring of R2a may be substituted.

R3 and R5 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, halo, OH, $ heterocyclyl.

(5).

Compound wherein, R1a is hydrogen, alkyl, alkoxy, OH, halo, NO2 or NH2.

R2a is hydrogen, (substituted) alkyl, cycloalkyl, alkoxy, (substituted) alkenyl, (substituted) alkynyl, (substituted) aryl, (substituted) heterocyclyl, alkoxy NRR, NO2, OH, NH2 or (substituted) heteroaryl.

R3 and R4 are each independently hydrogen, alkyl, aryl, cycloalkyl, OH, halo, amino, nitro.

R5 is hydrogen, (substituted) alkyl, cycloalkyl, aryl, (substituted) heterocyclyl, halo, OH or (substituted) heteroaryl.

(6).

Compound wherein, R2a is lower alkylene or lower alkenylene substituted by substituted acetyl or heterocycle.

R3 is optionally substituted phenyl.

(7).

Compound wherein, R1a, R2a are each independently hydrogen, halogen, (substituted) alkyl, (substituted) alkenyl, (substituted) aryl, (substituted) aralkyl, (substituted) heterocyclic group or alkylene groups same as.

R3 is optionally substituted amino

(8).

R1a is hydrogen, alkyl, cycloalkyl, alkoxy, -(alkyl) amino, aryl or heteroaryl.

R2a is hydrogen, alkyl, halogen, cyanogen, hydroxy or alkoxy.

R3 is optionally substituted amino or optionally substituted alkoxy.

R5 is aryl.

(9).

Compound wherein, R1a was substituted by group selected from the group comprising carboxy, lower alkoxy carboxy and substituted carbamoyl as substituent and is lower alkyl, and R2a is hydrogen.

R3 is phenyl carbonylamino, and the said phenyl group may be substituted.

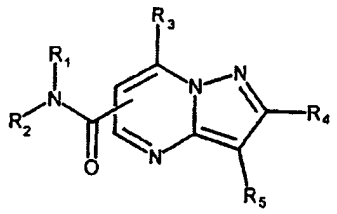
R4 and R5 are hydrogen.

(10).

(2,5-dimethylpyrazolo [1,5-a] pyrimidine-7-yl) succinic acid, wherein (the substituent which is not defined of among compound described in (1)-(10) denotes an arbitrary substituent).

2. Compound in accordance with Claim 1 that one or both of R1a and R2a is hydrogen, and the other is optionally substituted carbamoyl.

3. Compound in accordance with Claim 1 represented by formula



(I)

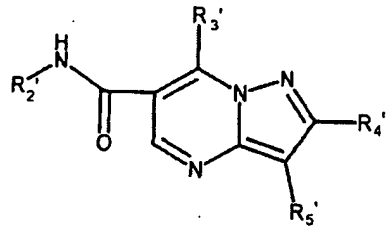
a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. (wherein, R1 is hydrogen, lower alkyl optionally substituted amino or optionally substituted aryl lower alkyl and R2 are hydrogen, optionally substituted lower alkyl optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl optionally substituted aryloxy l, optionally substituted lower alkyl sulfonyl, optionally substituted aryl sulfonyl, optionally substituted heteroaryl lower alkyl optionally substituted heterocyclic group lower alkyl or optionally substituted amino.

Or R1 and R2 comprises together with adjacent N atom, and optionally substituted heterocycle may be formed.

R3 is hydrogen, hydroxy, lower alkoxy, halogen or optionally substituted amino.

R4 is hydrogen, lower alkyl or optionally substituted aryl.

R5 is hydroxy, optionally substituted lower alkyl optionally substituted aryl, optionally substituted aryl lower alkyl optionally substituted cycloalkyl lower alkyl, optionally substituted aryl lower alkenyl, optionally substituted cycloalkyl lower alkenyl, optionally s, optionally substituted cycloalkyl lower alkynyl, optionally substituted aryl carbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted heterocyclic group, halogen, CH0, optionally substituted amino or optionally substituted imino. But wherein compounds of following formula are excluded



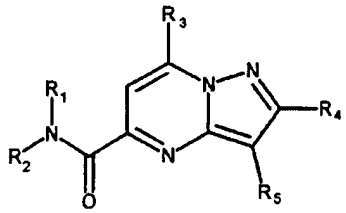
(I')

(wherein, R2' is the phenyl which may be substituted by hydrogen, lower alkyl or halogen, and R3 'is hydrogen or hydroxy.

R4 'is hydrogen or lower alkyl.

R5 'contains phenylthio group, and is the phenyl which may substitute by lower alkyl or lower alkoxy furthermore).

4. Compound in accordance with Claim 3 represented by formula



(I-1)

(same meaning the aforesaid each substituent), a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein.

5. Compound described in Claim 3 or 4 &. A prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. R1 is hydrogen.

R2 is optionally substituted aryl.

6. Compound, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein are described in Claim 3 or 4 &. R3 is hydrogen or the amino which may be substituted.

7. Compound, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein are described in Claim 3 or 4 &. R4 is hydrogen.

8. Compound, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein are described in Claim 3 or 4) . R5 is optionally substituted aryl.

9. Compound, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein are described in Claim 3 or 4 &. R1 is hydrogen and R2 is optionally substituted phenyl.
R3 is hydrogen or the amino which may be substituted and R4 is hydrogen.
R5 is optionally substituted phenyl.

10. Compound in accordance with Claim 9, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. Substituent is at least one which is selected from the group which comprised optionally substituted heterocyclic group, lower alkyl carbonyl, cycloalkyl, lower alkyl optionally substituted amino, halogen, halogenation lower alkyl, lower alkoxy, carboxy lower alkyl oxy, heterocyclic group lower alkyl oxy, amino lower $$$, hydroxy, cyanogen, carbamoyl heterocyclic group oxy, cyano lower alkyl and phenyl in the phenyl which may be substituted of R2.

11. Compound in accordance with Claim 10, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. R2 is optionally susbstituted heterocyclic group phenyl.

12. Compound in accordance with Claim 10, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein. R2 is optionally substituted piperazino phenyl, optionally substituted piperidino phenyl or the pyrrolidino phenyl which may be substituted.

13. Compound in accordance with Claim 9 which is at least one which is selected from the group that substituent comprised halogen, halogenation lower alkyl, aryl lower alkyl oxy, lower alkyl, lower alkoxy, hydroxy, lower alkyl thio, phenyl, phenyloxy, phenyl lower alkyl, phenyl lower alkyl amino, phenyl lower alkyl thio, phenyl lower alkenyl, phenylcarbamoyl, amino, cycloalkyl lower alkyl oxy and heteroaryl lower alkyl oxy in the phenyl which R5 might substitute, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein.

14. Compound in accordance with any of Claim 1-13 is contained and is medicinal composition.

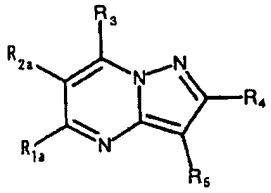
15. Compound in accordance with any of Claim 1-13 is contained and is NAD(P) H oxidase inhibitor.

16. Preventative agent of disease compound in accordance with any of Claim 1-13 is contained, and to be related to NAD(P) H or therapeutic agent.

17. Preventative agent or therapeutic agent in accordance with Claim 16 which is selected from the group which a the aforesaid disease damaged inflammation, disturbance of pulmonary circulation, ischemic cardiac disease, cerebral circulation, and comprised arteriosclerosis, diabetes mellitus complication, hypertension and proliferation associated disease.

18. Preventative agent or therapeutic agent in accordance with Claim 16 that a the aforesaid disease is cerebral infarction or diabetic retinopathy.

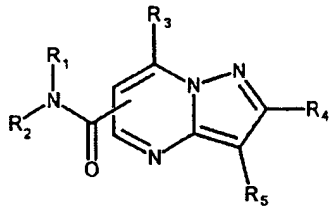
19. Compound represented by



(1a)

, prodrug thereof, pharmaceutically permitted salt thereof or solventate thereof is contained and is NAD(P)H oxidase inhibitor. (wherein, R1a, R2a, R3-R5 each independently show hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted heterocyclic group, hydroxy, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted heterocyclic oxy, optionally substituted acyl, optionally substituted monosubstituted carbonyl oxy, optionally substituted carbamoyl, diazo, optionally substituted amidine, azide, two thoron, nitro, optionally substituted amino, optionally substituted imino, cyanogen, mercapto, optionally substituted monosubstituted thio, optionally substituted monosubstituted thio oxy, optionally substituted monosubstituted sulphinyl, optionally substituted monosubstituted sulfonyl, sulfo or tri substituted silyl, and R1a, R2a, R3-R5 each independently link together by an arbitrary combination, and it may be formed a ring structure).

20. Compound represented by



(I)

, prodrug thereof, pharmaceutically permitted salt thereof or solventate thereof is contained and is NAD(P)H oxidase inhibitor. (wherein, R1 is hydrogen, lower alkyl optionally substituted amino or optionally substituted aryl lower alkyl and R2 are hydrogen, optionally substituted lower alkyl optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl optionally substituted aryloxy l, optionally substituted lower alkyl sulfonyl, optionally substituted aryl sulfonyl, optionally substituted heteroaryl lower alkyl optionally substituted heterocyclic group lower alkyl or optionally substituted amino.

Or R1 and R2 comprises together with adjacent N atom, and optionally substituted heterocycle may be formed.

R3 is hydrogen, hydroxy, lower alkoxy, halogen or optionally substituted amino.

R4 is hydrogen, lower alkyl or optionally substituted aryl.

R5 is hydroxy, optionally substituted lower alkyl optionally substituted aryl, optionally substituted aryl lower alkyl optionally substituted cycloalkyl lower alkyl, optionally substituted aryl lower alkenyl, optionally substituted cycloalkyl lower alkenyl, optionally s, optionally substituted cycloalkyl lower alkynyl, optionally substituted aryl carbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted heterocyclic group, halogen, CH0, optionally substituted amino or optionally substituted imino.

21. Process for the therapy or prevention of disease it is characterised in that, and to be related to NAD(P) H to administer effective dose of compound in accordance with any of Claim 1-20 to animal including human being.

22. Process in accordance with Claim 21. Wherein, a the aforesaid disease is selected from the group

which comprised inflammation, disturbance of pulmonary circulation, ischemic cardiac disease, Masaru circulatory disease, arteriosclerosis, diabetes mellitus complication, hypertension and proliferation associated disease.

23. Process in accordance with Claim 21 that a the aforesaid disease is cerebral infarction or diabetic retinopathy.

24. Use of compound in accordance with any of Claim 1-20 to produce pharmaceutical to be used in order to do prevention or therapy of a disease to be related to NAD(P) H.

25. Use in accordance with Claim 24. Wherein, a the aforesaid disease is selected from the group which comprised inflammation, disturbance of pulmonary circulation, ischemic D disease, cerebral circulation disorder, arteriosclerosis, diabetes mellitus complication, hypertension and proliferation associated disease.

26. Use in accordance with Claim 24 that a the aforesaid disease is cerebral infarction or diabetic retinopathy.

The following text comprises an amendment of the last page with the intention of adding Claim s27 to30.

This amendment was made on the 8th August2003.

21.Tail end of Claim 22..

23. Process in accordance with Claim 21 wherein, an aforesaid disease is cerebral infarction or diabetic retinopathy.

24. Use of compound in accordance with any of Claim s 1-20 to produce pharmaceutical to be used so that prevention or therapy makes a disease to be related to NAD(P) H.

25. An aforesaid disease is use in accordance with Claim 24 selected from the group which comprised

inflammation, disturbance of pulmonary circulation, ischemic cardiac disease, cerebral circulation disorder, arteriosclerosis, diabetes mellitus complication, hypertension and proliferation associated disease.

26. An use in accordance with Claim 24 wherein, an aforesaid disease is cerebral infarction or diabetic retinopathy.

(added)
27. A compound in accordance with Claim 1, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein R1a is optionally substituted carbamoyl.

(added)
28. A compound in accordance with Claim 1, a prodrug thereof, a pharmaceutically acceptable salt thereof or a solventate thereof wherein R1a. is optionally substituted carbamoyl, R2a are hydrogen

(added).
29. A drug containing a compound in accordance with Claim 27 or 28.

(added).
30. NAD(P)H oxidase inhibitor containing a compound in accordance with Claim 27 or 28.

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